ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/303673576

The Root Cause in the dramatic rise of Chronic Disease

Article · May 2016

CITATIONS
0

READS
4,389

1 author:



Richard Lear
Brown University
5 PUBLICATIONS **0** CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Dramatic Rise in Chronic Disease View project

All content following this page was uploaded by Richard Lear on 10 September 2018.

The user has requested enhancement of the downloaded file.

The Root Cause in the dramatic rise of Chronic Disease

Richard A. Lear
richardlear@alumni.brown.edu
August 2016/ 2018

NOTE to Readers: There has been a largely unrecognized explosion of chronic disease in the US. More than 170 million Americans may already be suffering from diseases and medical conditions that can be vastly improved or even reversed by reducing levels of a single molecule called peroxynitrite. Elevated levels of peroxynitrite has been associated with more than 60 chronic diseases. Additionally six concomitant biofactors arise across 36 fast-growing germless, diseases, all of which are linked to peroxynitrite. The coincidence of these six biological factors suggests the existence of a coherent biological system that both defines the chronic disease state, and possibly predicts the coming onset of disease. It should be no surprise that chronic inflammation, oxidative stress (OX) and mitochondrial dysfunction are among the six biofactors. All three are popularly known for their association with and possible causative effect in chronic disease. Yet, the lesser-known, nitrative stress (NOX), may actually be the most devastating of all six to biochemical integrity and overall homeostasis.

The initial purpose of this paper was to estimate the scope, scale, trends and economic costs of the fastest growing chronic diseases in the US. Most of us have witnessed first-hand the terrible emotional and financial costs that chronic disease has imposed in our own lives. Yet something larger may be in play. The convergence of the science that suggests a possible *disease state,* which we call *P-factor,* may offer three breakthrough avenues for research:

- Can a *unifying theory* of chronic, germless disease be confirmed?
- If there truly exists a definitive biological model, or coherent mechanism for the disease state as the science suggests, can it be successfully leveraged for clinical diagnostics and possible cures?
- If the endogenous (internal) mechanism for disease can be established, what are the exogenous (external) triggers?

The science community already recognizes the pivotal role of peroxynitrite in disease. Yet, few policy makers and physicians are aware of the opportunity they have to heal a nation suffering from chronic diseases. It seems, the message is not getting through. As a result, government research for peroxynitrite and many of the diseases listed in this paper is modest at best. While few initiatives are considering a "unifying theory" of disease, the promise of such a theory is now better than ever. Meanwhile, most physicians are not sufficiently equipped to cure most chronic diseases. Yet, there exists in nature more than 20 scavengers of peroxynitrite. The promise of leveraging existing science to find remedies and cures for chronic disease is already a reality.

The *annual* economic burden of just thirty-six fast-growing chronic diseases tracked in this paper is more than $2.77 trillion. With dedicated research on the mechanisms and cures for chronic, germless disease, this cost to society can be reduced to a fraction – by simply acting on the knowledge we already have.

Growth of Chronic Disease

There has been unprecedented growth in chronic disease in the US since 1990. Four new categories of disease have virtually exploded: autoimmune, neurological, metabolic and inflammatory. Meanwhile, there has been a similar uptick in reproductive conditions like infertility and half dozen psychiatric disorders.

While the major health threats of the 20th century - cardiovascular disease, infectious disease and cancer - are barely growing, at least 36 chronic diseases and disorders have more than doubled in the past generation. Twenty have more than tripled. Many of these *new age* diseases were unknown until the 1980s. Here is a sampling of the growth in prevalence of diseases and disorders: autism (2094%), Alzheimer's (299%), COPD (148%), diabetes (305%), sleep apnea (430%), celiac disease (1111%), ADHD (819%), asthma (142%), depression (280%), bipolar disease – youth (10833%), osteoarthritis (449%), lupus (787%), inflammatory bowel disease (120%), chronic fatigue syndrome (11027%), fibromyalgia (7727%), multiple sclerosis (117%) and hypothyroidism (702%).

Method and Comment

The disease metrics found in this paper were derived from the scientific literature. Our research primarily draws from studies cited or published by the Centers for Disease Control (CDC), PubMed, NCBI and/ or the National Institutes of Health (NIH). When we found data for some diseases were out of date – more than five years old – we supplemented our data from scientific studies from other nations, including Canada, the UK, Ireland and Denmark. Through our research we discovered the existence of a generally *unrecognized epidemic* of chronic disease, which we estimate affects more than 170 million Americans.

The statistics cited here are often built on estimates. That they are over-precise is a given. These include *estimated* increases in prevalence, growth and economic costs of disease. As there exists a paucity of statistics for many diseases studied here, we have adopted a convention called *generational growth* to normalize growth of disease across the 25-year period. See the section on *Generational Growth* below for details.

The metrics which follow are offered to provide greater visibility into the scale, trajectory and economic impact of this unfolding societal problem. While it is our core objective to convey the *order of magnitude* for this rise in chronic disease, it is likely that these metrics understate the actual size and breadth of the health crisis currently plaguing the US. Folowing, you will find a breakdown of 36 chronic diseases and and conditions which have

have experienced exponential growth over the most recent generation:

36 Diseases have more than doubled in the US – 1990 - 2015

ADD/ ADHD	Allergies	Alzheimer's	Anxiety	Asthma	Autism
139%	104%	299%	104%	142%	2,094%
Autoimmune Disease	Bipolar Disorder (youth)	Cataracts	Celiac Disease	Chronic Fatigue	Congenital Heart Disease
221%	10,833%	480%	1,111%	11,027%	143%
COPD	Depression	Diabetes	Erectile Dysfunction	Fibromyalgia	Inflammatory Bowel (IBD)
148%	280%	305%	150%	7,727%	120%
Hypertension	Kidney Stones	Kidney Disease	Leukemia	Lupus (SLE)	Melanoma
223%	246%	413%	588%	787%	145%
Multiple Sclerosis	Obesity	Osteoarthritis:	Panic Disorder	Psycho-Social: Attentional	Psycho-Social: Emotional
117%	260%	449%	263%	819%	2,500%
Sleep Apnea	Sleep: Insomnia	Squamous Cell Cancer	Stroke	Thyroid Dysfunction	Hypothyroidism
430%	123%	177%	262%	233%	702%

The *Smoking Gun*

While controversy remains over possible external causes, one internal biological trigger may already be known. A single molecule produced by the body called *peroxynitrite* is associated with every disease and chronic condition tracked in this paper. In January 2007 three leading scientists, funded by the National Institutes of Health (NIH), published, "Nitric Oxide and Peroxynitrite in Health and Disease,"[1] This paper details the massive destructive capabilities of peroxynitrite ($ONOO^-$).

The lead author, Dr. Pal Pacher, who has published 260 peer-reviewed papers, is among the top 50 most-cited researchers in the pharmacology and toxicology fields worldwide. Ph.D's Joseph Beckman and Lucas Liaudet join him on this paper. Beckman is Principal Investigator and Burgess and Elizabeth Jamieson Chair in Healthspan Research, Linus Pauling Institute at Oregon State University. Lucas Liaudet, who is affiliated with University Hospital at Lausanne, has published more than 200 peer-reviewed papers with over 10,000 citations.

Together, this elite scientific team details the cytotoxic effects, tissue damage and biochemical disruption of peroxynitrite. In their landmark paper, they connect the molecule to more than 60 chronic diseases. Among them: neurodegenerative disorders, heart disease, vascular disease, accelerated aging, hypertension, inflammatory disease, cancer, stroke, arthritis, IBS, kidney disease, liver disease, Alzheimer's, MS and diabetes.

Until now many in the scientific community have been reticent to propose a unifying factor that explains the dramatic rise of so many seemingly unrelated diseases. Yet, there is growing evidence that peroxynitrite may just be that elusive *factor*. I recently asked Dr. Pacher, if it would be hyperbole to call peroxynitrite the "smoking gun" for chronic disease. Without hesitation he replied, "Absolutely not!"

Peroxynitrite acts as both an *oxidative* and *nitrative* agent, causing extensive cellular damage, while disrupting at least 97 *critical* biological processes (see appendix). This molecule is set loose by the combination of two free radicals, one of which is nitric oxide ($NO^{\cdot}$). Among the most studied molecules in the body, nitric oxide is known to be a critical component of numerous biological processes, most notably vascular dialation. When found in close proximity, it combines with superoxide ($O2^{\cdot}$) to create peroxynitrite ($ONOO^{-}$). In turn, peroxynitrite catapults our sensitive biochemistry into unimaginable chaos.

Left unchecked, *peroxynitrite* single-handedly creates high levels of oxidative stress (OX)[1], nitrative stress (NOX)[1], mitochondrial dysfunction (MD)[1] and autonomic dysfunction (AD) while triggering *cytokine storms*, which then lead to chronic systemic inflammation (CI)[1]. By stealing electrons from important biological actors like lipids (essential fats), proteins and enzymes, peroxynitrite wreaks havoc on cellular integrity and function. It degrades ATP (cellular energy) production, which robs the brain and other organs of energy and creates palpable fatigue. It interferes with ion messaging, which causes toxity at the cellular level and interferes with the autonomic nervous sytem, causing panic moments and heart palpitations.

Meanwhile peroxynitrite interferes with production of at least two key neurotransmitters – dopamine and serotonin. Low levels of these neurotransmitters are associated with depression, mood swings, poor concentration, low motivation, aggression, irritability and even violence. Meanwhile this prolific anion damages DNA, which leads to genotoxic effects – the inability to replicate cells - and cultivates a biological environment for disease.

P-Factor: the *Chronic Disease State*

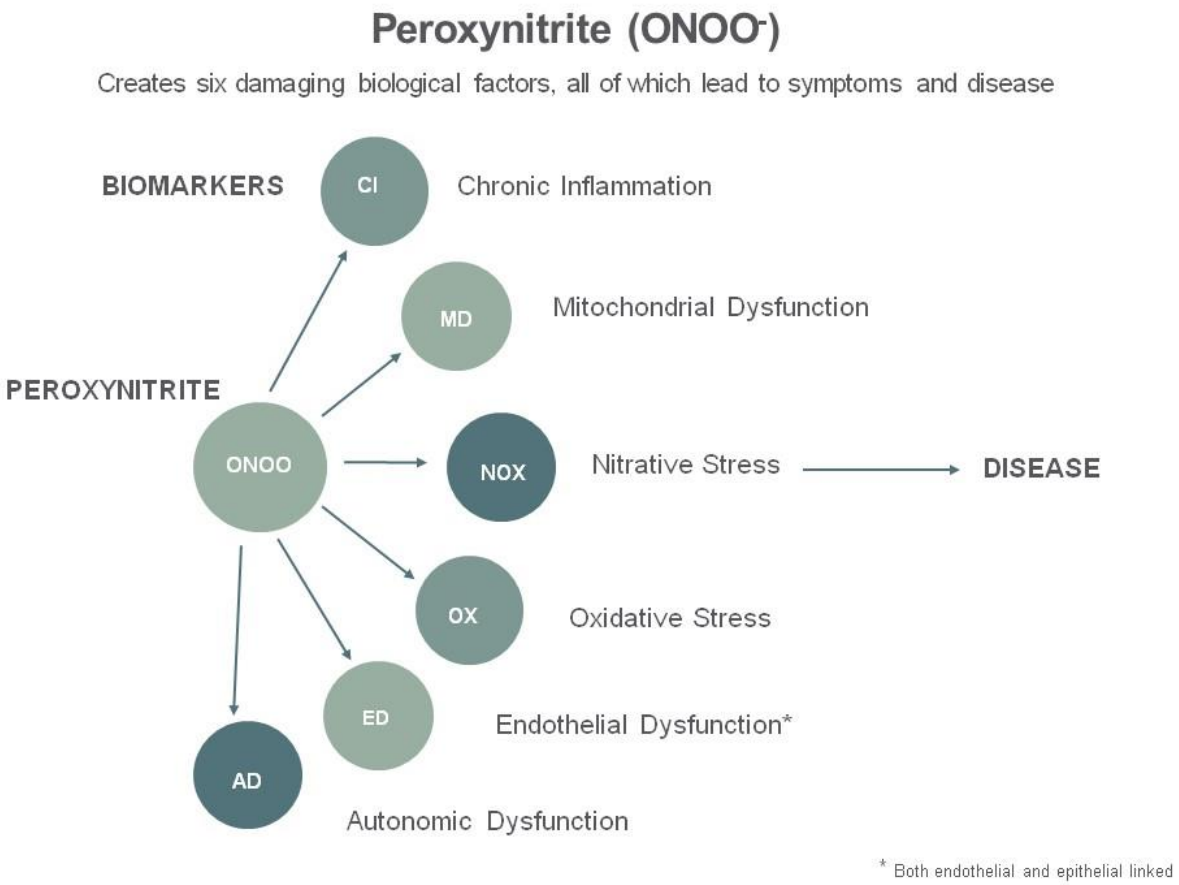
Our research examines forty fast-growing diseases and conditions, which were found to share a common biological profile. For easier statistical comparison, our main focus is on 36 diseases and conditions. We call this biological profile - *P-Factor*. Each of the six biofactors that comprise P-Factor is strongly associated with all 36 of the fast-growing diseseases. The science also confirms that each biofactor appears to be either triggered by or accelerated through interactions with peroxynitrite.[1]

The following biofactors are common constituents of the *chronic disease state* we call P-Factor. (See Table 1):

- Oxidative Stress (OX)
- Nitrative stress (NOX)
- Chronic Inflammatory State (CI)
- Mitochondrial Dysfunction (MD)
- Autonomic Dysfunction (AD)
- Epithelial/ Endothelial Dysfunction (ED)

In their paper, *Pacher et al* build *the* theoretical case for how a complex series of biochemical disruptions, triggered by peroxynitrite, sets in motion a lethal combination of *oxidative* and *nitrative stress*. The NIH paper rigorously puts forth that the proliferation of free radicals (OX) and nitrative agents (NOX) like *nitrotyrosine* disrupt a broad array of biological systems, which, in turn, leads to a self-reinforcing *vicious cycle* of chronic inflammation (CI), mitochondrial dysfunction (MD) and epitheilial/endothelial dysfunction (ED).

The expected outcome predicts disequilibrium, biological damage and the emergence of disease. The graphic below shows the key elements of the chronic disease state, each factor scientificially demonstrated to be triggered by peroxynitrite. The real-world disease outcomes found in this paper serve to confirm the theoretical constructs put forth by the NIH metastudy in addition to hundreds of studies cited in the paper.



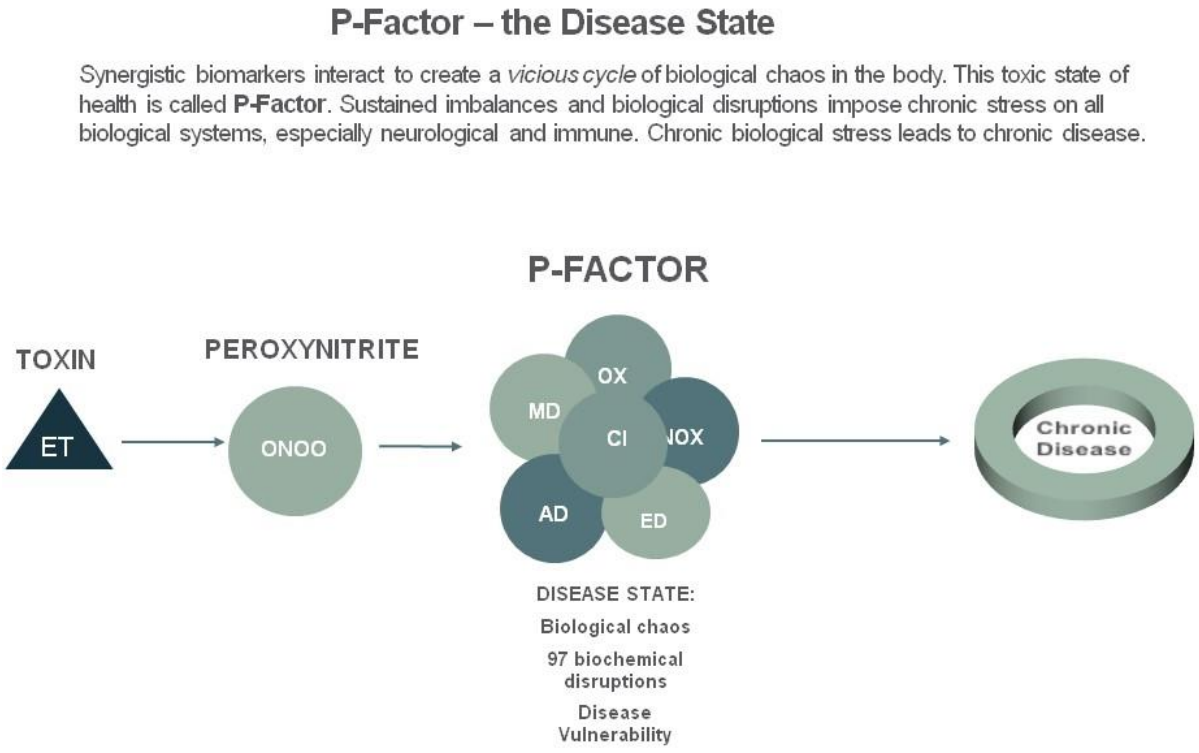
P-Factor Synergies and the Vicious Cycle

Both the presence of these six biofactors and the complex interactions between them lead to a chaotic and pathological biochemical environment that affects multiple biological systems. Scientists have linked neurological impacts, elevated immune system activity and inflammatory disease to all six components of P-Factor. Most troubling are internally synergistic biological cycles created by the interaction of the biofactors.

Many of these biofactors activate others and some even create higher levels of peroxynitrite themselves. Both actions serve to reinforce and even accelerate the cycle of disease. For instance, peroxynitrite creates reactive oxygen species (ROS), which can then trigger chronic inflammation. This inflammation acting through NF-κB activates an immune system response, which, in turn, creates increased levels of nitric oxide, which then creates more peroxynitrite. Then a new reinforcing cycle begins. In other reactions, peroxynitrite may create oxidative stress (OX) or nitrative stress (NOX), both of which can then disrupt the electron transport chain process in the mitochondria. The result is mitochondrial

dysfunction (MD) – a diminished capacity of the mitochondrion to do its job. The mitochondria, which should act like a virtual factory for cellular energy (ATP), suddenly change their production line. Instead of producing cellular energy, the mitochondria begin producing less energy and ironically, more harmful peroxynitrite. The cycle then repeats.

The self-sustaining properties of P-Factor created through reinforcing synergies between biofactors, which then lead to vicous cycles, help explain why *chronic* diseases are chronic.



DATA on Chronic Disease and Medical Conditions

In our survey of the literature, the real life drama plays out precisely as Pacher, Beckman and Liaudet have predicted. We are now facing an alarming level of fast-growing diseases for which there has been no warning. Peroxynitrite sits conspicuously at the heart of this unexpected health epidemic. A single prolific molecule emerges as a central antagonist and prime mover in the unprecedented rise in chronic disease. The synchronicity of the *theoretical* science on peroxynitrite and the extraordinary real-world impacts we have experienced to human health leaves little question as to the root cause in the dramatic rise in chronic disease in the US.

The following data track the extraordinary scope of the chronic disease phenomenon in the US. It highlights the actual number of reported cases for the thirty-six fast-growing diseases.

679,755,450 reported cases in 36 fast-growing diseases

Disease	Reported	Disease	Reported	Disease	Reported
ADD/ADHD	5,312,000	Congenital Heart Disease* (CHD)	2,000,000	Lupus	563,542
Allergies (food)	16,474,300	COPD	3,862,335	Melanoma	996,587
Alzheimer's	4,700,000	Depression	20,304,560	Multiple Sclerosis	2,100,000
Anxiety	40,000,000	Diabetes (I&II)	29,100,000	Obesity	110,736,980
Osteoarthritis	27,000,000	Diabetes type I	incl. above	Panic Disorder	6,000,000
Asthma	25,500,000	Erectile Dysfunction	18,000,000	Sleep Disorders	100,825,520
Autism	4,664,280	Fibromyalgia	6,345,959	Sleep Apnea	50,160,693
Autoimmune Disease	24,114,643	Inflammatory Bowel Disease (IBD)	1,150,000	Allergic Rhinitis	60,000,000
Bipolar Disorder (youth)	768,481	Hypertension	92,799,900	Sleep: Insomnia	48,396,250
Cataracts	20,500,000	Kidney Stones	28,620,000	Squamous Cell Cancer	322,762
Celiac Disease	3,000,000	Kidney Disease: ESRD	871,000	Stroke	6,800,000
Chronic Fatigue (CFS)	8,077,200	Leukemia	327,520	Thyroid Dysfunction	20,000,000

Generational Growth

This paper tracks the growth of chronic disease from 1990-2015 – a single generation. One challenge in calculating growth across a generation arises from the paucity of data available that precisely covers this 25-year period. Consequently, our best sources provide data, which samples *partial* time segments during this period.

As a means for revealing the underlying secular growth of the prevalence of disease, we have adopted a metric we call *Generational Growth*. This metric serves to normalize the data for comparison by extrapolating growth across partial time intervals to reflect expected growth over the full 25-year period. In some cases this approach may overestimate actual growth; and in others it may underestimate it. As mentioned earlier, it is not the objective of this paper to precisely measure empirical growth in chronic disease; but rather to demonstrate an order of magnitude of the dramatic rise across broad categories of chronic disease. One final anomaly: as mentioned earlier, much of the data utilized in our calculations are in

themselves statistical estimates for the prevalence of disease. Thus tracking growth, using estimates of both beginning and ending statistics is inherently challenging. Nonetheless, for those who remain skeptical of the exponential growth of chronic disease in the US, a cursory review of growing health care costs, pharmaceutical drug sales, lost productivity, physician visits and the extraordinary acceleration of multiple chronic conditions should confirm this unprecedented trend.

Secular Trends

On balance the data reveal an accelerating rising trend for autoimmune, inflammatory, metabolic and neurological/ neurodegenerative diseases that cannot be simply explained by an aging population. Nor can it be easily explained by a trend within the medical community to more aggressively diagnose chronic disease and disorders. The uptick in a new class of chronic diseases and disorders confirms what most of us have already been observing within our own families and communities for some time.

It should be noted that this paper primarily tracks the *prevalence* of disease but where these statistics are unavailable or not appropriate, we employ *incidence* statistics. Prevalence measures the percentage (%) of the population currently affected by each disease. Incidence signifies the percentage of new cases reported each year. The percentages listed in Table 1 represent absolute changes in proportions over a particular time interval, which vary.

Economic and Societal Impacts

The economic and social impacts from these new diseases are substantial. The US is spending more than $2.7 trillion annually across just 36 fast-growing diseases that have more than doubled in a generation. This represents the *first order* of the economic burden, which includes medical costs, lost income and research funding.

Subsequent economic inefficiencies rapidly accrue to an economy with millions of people trying to work and recreate, who are facing suboptimal health. The human suffering and societal costs are incalculable. Conservative estimates show more than 679 million reported cases of these fast-growing chronic diseases across the US population by 2016. The human factor cannot be quantified.

The *reported cases* figures are provided for each of the forty diseases and disorders but likely underestimate actual levels. The data in our chart reflect statistics that both precede the publication date of each study and some that are already several years out of date. Both factors serve to underestimate current levels, especially for dramatically growing diseases.

Annual Cost of 32 fast-growing diseases: **$2.7+ trillion.**

Disease	Cost (B)	Disease	Cost (B)	Disease	Cost (B)
ADD/ADHD	$204.50	Congenital Heart Disease* (CHD)	$78.70	Melanoma	$3.35
Allergies (food)	$24.88	COPD	$50.10	Multiple Sclerosis	$10.10
Alzheimer's	$227.20	Depression	$192.30	Obesity	$215.90
Anxiety	$42.30	Diabetes (type I&II)	$246.00	Allergic Rhinitis	$17.51
Osteoarthritis	$153.30	Diabetes type II	included above	Sleep Apnea	$420.00
Asthma	$62.10	Erectile Dysfunction	$1.00	Sleep: Insomnia	$113.90
Autism	$268.20	Fibromyalgia	$37.70	Stroke	$34.30
Autoimmune Disease	$100.80	Inflammatory Bowel Disease (IBD)	$11.90	Thyroid Dysfunction	$4.30
Bipolar Disorder (youth)	$151.00	Hypertension	$73.60	TOTAL:	
Cataracts	$10.70	Kidney Stones	$5.30	**$2,777,690,000,000**	
Celiac Disease	$24.65	Kidney Disease: ESRD	$32.00		
Chronic Fatigue (CFS)	$51.00	Lupus	$9.90		

Deriving Estimates for Affected Population

Let's assume all 92.8 million hypertension sufferers also suffer from obesity and sleep disturbances. This leaves a little more than 400 million reported cases across the remaining 229 million Americans. Now let us assume at least 60% of the remaining people have no chronic illness. That leaves about 80 million people to distribute over the 400 million reported cases. This implies a penetration chronic disease of 172.8 million Americans. Even if our first *very conservative* assumption is correct, it is pretty doubtful that 80 million Americans have an average of five of the 36 fast-growing diseases and chronic conditions. As such, the data suggest at least 170 million people are affected by at least one of the chronic diseases studied here.

170 million equates to approximately 53% of the US population. As context, the CDC reports that 48.7%[2] of the population has taken a prescription drug in the past 30 days.

Conclusion:

The initial purpose of this paper was to estimate the scope, scale, trends and economic costs of the fastest growing chronic diseases in the US. Most of us have witnessed first-hand the terrible emotional and financial costs that chronic disease has imposed in our own lives. Yet something larger may be in play. The convergence of the science that suggests a possible *disease state,* which we call *P-factor,* may offer three breakthrough avenues for research:

- Can a *unifying theory* of chronic, germless disease be confirmed?
- If there truly exists a definitive biological model, or coherent mechanism for the disease state as the science suggests, can it be successfully leveraged for clinical diagnostics and possible cures?
- If the endogenous (internal) mechanism for disease can be established, what are the exogenous (external) triggers?

While thousands of scientists recognize the pivotal role of peroxynitrite in disease, few policy makers and physicians are aware of the opportunity they have to heal a nation suffering from chronic diseases. It seems, the message from the science is not getting through. As a result, government research for peroxynitrite and many of the diseases listed in this paper is modest at best. While few initiatives are examining "unifying theories" of disease, the promise of such a theory is better than ever. And the stakes are higher than ever. Meanwhile, most physicians are not sufficiently equipped to cure most chronic diseases. Yet, there exists in nature more than twenty scavengers of peroxynitrite. While many pharmaceutical companies may be reticent to tap this resource, the possibility of leveraging existing science to find remedies and cures for the Diseases of Civilization is already a reality.

The *annual* economic burden of just thirty-six fast-growing chronic diseases tracked in this paper is more than $2.77 trillion. This is more than 70% of the current annual federal budget. With increased public awareness, coupled with a federal government commitment to dedicated research on the mechanisms and cures for the Diseases of Civilization, this cost to society can be reduced to a fraction – by simply acting on the knowledge we already have.

Master Table – Research

The Table 1 below tracks growth and scale of disease and economic statistics for forty chronic diseases and medical conditions. Thirty-six have more than doubled in the past 25 years. It demonstrates the concentration of four new classes of chronic disease and medical conditions, which have dramatically risen since 1990. The focus of this paper has been to identify and examine germless, chronic diseases that share the following common factors:

- Each more than doubled in prevalence since 1990. *
- Each is associated in scientific studies with:
    - Peroxynitrite
    - Oxidative Stress (OX)
    - Nitrative Stress (NOX)
    - Mitochondrial Dysfunction (MD)
    - Chronic Inflammation (CI)
    - Autonomic Dysfunction (AD)

As discussed earlier, the following data track the *generational growth* of forty chronic diseases and conditions, the scale of those affected; plus key economic costs associated with the thirty-six fast-growing diseases and conditions.

Table 1.

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxynitrite	NOX-Tyrosine Nitration	OX	CI	MD	AD
1	Neurological[3]	**ADD/ ADHD**	5,312,000[4]	139%[4]	204.5[5,6]	204.5[7]	42.5[8,9]	N/A	.045[6]	1[10]	1[10]	3[10,11,12]	1[13]	1[14]	1[15]
2	Inflammatory	**Allergic Rhinitis**	60,000,000[16]	79%[17]	17.51[6,18]	17.5[18]	17.5[18]	N/A	.006[6]	2[19,20]	3[16,20,21]	2[16,22]	2[16,22]	1[23]	1[24]
3	Inflammatory	**Allergies - Food**	16,474,300[25]	104%[25]	24.88[6,26]	24.8[26]			.035[6]	1[16]	1[16]	1[27]	2[28,29]	1[30]	1[31]
4	Neurological[32]/ Inflammatory[33]	**Alzheimer's**	4,700,000[34]	299%[34,35]	227.2[6,36]	226.6[36]	186[36]		.562[6]	12[1,37,38, 39,40,41,42 ,43,44,45, 46,47	9[37,38,39,41, 42,43,44,45, 46,47]	7[37,39,40 ,42,43,44, 47,48]	3[43,49,50]	4[43, 47,51,52, 53]	1[54]
5	Mental Health	**Anxiety**	40,000,000[55]	104%[55]	42.3[56]	42.3[56]				2[57,58]	1[59]	2[60,61]	1[62]	1[63]	1[64]
6	Mental Health	**Panic Disorder**	6,000,000[65]	263%[56,66]	Incl. In Anx. [56]	Incl. In Anx.[56]				1[58]	1[67]	1[60]	1[62]	1[63]	0
7	Inflammatory	**Osteoarthritis**	27,000,000[68]	449%[69]	153.3[70]	153.3[70]	83.6[70]	69.7[70]		4[71,72,73, 74	1[75]	1[76]	2[77,78]	1[79]	1[80]
8	Inflammatory	**Asthma**	25,500,000[81]	142%[81]	62.1[6,82]	61.9[82]	56[82]	5.9[83]	.241[6]	7[1,74,84, 85,86,87,88	4[74,84,88,89,	4[84,85,88, 90	3[84,88,91	1[92]	2[31,93
9	Neurological[94]	**Autism Spectrum Disorder**	4,664,280[95]	2094%[95, 96	268.2[6,97]	268[97]	126[97]		.188[6]	5[98,99,100 ,101,102	4[98,99,100,1 01	4[98,99,10 0,103	4[98,99,10 0, 103	3[98,100,1 03	1[104
10	Autoimmune	**Autoimmune Disease**	(24,114,643) [†105]	221%†	100.8[6,106]	100.8[106]	100[106]		.822[6]	9[1,46,74 ,107,108, 109,110, 111,112	7[46,75,107, 108,111,112 ,113	1[114]	2[107,115]	1[116]	1[117]
11	[Neurological] [118,119,120]	**Bipolar Disorder** (youth)	768,481[121]	10833%[1 21]	151.0[122]	151[122]	30.7[122]	120.3[122]		3[123,124, 125	2[124,125]	3[123,124, 126	3[123,126, 127	2[123,128]	1[129]
12	Vision	**Cataracts**	20,500,000 [130]	480%[130]	10.7[131]	10.7[131]	10.7[131]			7[132,133, 134,135,	5[135,136,138 ,139,140	3[133,134, 136,141	1[142]	1[143]	1[144]

† Autoimmune diseases tracked in this paper include Alzheimer's, Celiac, CFS, Type 1 Diabetes, Lupus, MS and IBD. Total affected for these diseases are tallied in the totals. However, the total affected listed for autoimmune disease is not included in final totals, as that number includes diseases not tracked in this paper. .

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxynitrite	NOX-Tyrosine Nitration	OX	CI	MD	AD
										[136,137,138]					
13	Autoimmune/ Inflammatory	**Celiac Disease**	3,000,000[145,146]	1111%[147]	24.65[6,148]	24.65[148]	24.65[148]			5[46,74,149,150,151]	4[46,149150,152]	1[149]	1[149]	1[153]	1[154]
14	Inflammatory	**Chronic Fatigue Syndrome**	8,077,200[155]	11027%[155,156]	51.0[6,157]	51[157]	14[157]	37[157]	.005[6]	5[158,159,160,161,162]	2[161,162]	2[162,163]	1[164]	2[162,165]	1[166]
15	Genetic	**Congenital Heart Disease* (CHD)**	2,000,000[167]	143%[168]	78.7[169]	78.7[169]	78.7[169]			1[170]	1[170]	1[171]	1[172]	1[173]	1[174]
16	Inflammatory [175]	**COPD**	3,862,335[176]	148%[176]	50.1[6,177]	50[177]	30[177]	20[177]	.107[6]	9[178,179,180,181,182,183,184,185,186]	7[178,179,180,181,182,183,187]	1[188]	1[189]	1[190]	1[191]
17	Mental Health	**Depression**	20,304,560 [192]	280%[192]	192.3[6,193]	191.9[193]	86.4[193]		.396[6]	5[194,195,196,197,198]	3[194,195,196]	4[198,199,200,201]	4[195,200,202,203]	3[199,200,204]	1[205,]
18	Metabolic	**Diabetes Mellitus**	29,100,000 [206]	305%[207]	246.0[6,208]	245[208]	176[208]	69[208]	1.011[6]	10[1,71,209,210,211,212,213,214,215,216]	8[46,210,211,212,213,214,217,218]	2[211,219]	2[220,221]	2[211,222]	1[223]
19	Autoimmune [224]/ Metabolic	**Diabetes Type 1**	Incl. in Diabetes Mellitus[206]	144%[225]	Incl. in Diabetes Mellitus[6,208]	Incl. in Diabetes Mellitus [208]	Incl. in Diabetes Mellitus [208]		Incl. in Diabetes Mellitus [6]	9[1,46,74,209,210,211,213,214,216]	6[46, 210,211,213,214,218]	1[226]	1[227]	1[222]	1[228]
20	[Neurological] [229][Inflammatory][230]	**Erectile Dysfunction**	18,000,000	150%[231]	1.0[232]					5[233,234,235,236,237]	3[233,234,235]	1[238]	1[239]	1[240]	1[241]
21	Neurologic[242,243]	**Fibromyalgia**	6,345,959[244]	7727%[6,245]	37.7[246]	37.7[246]	37.7[246]		.010[6]	2[158,247]	2[158,247]	1[248]	1[249]	1[248]	1[250]

* It is thought that the growth in prevalence of congenital heart disease may be largely due to increased longevity.

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxynitrite	NOX-Tyrosine Nitration	OX	CI	MD	AD
22	Autoimmune/ Inflammatory	**Inflammatory Bowel Disease (IBD)**	1,150,000[251]	120%[6,252]	11.9[6,253, 254]	11.8[254]	6.3[254]	5.5[253]	.125[6]	8[1,74,112, 255,256, 257,258, 259]	5[112,255,256 ,257,260]	2[257,261]	2[257,262]	2[263,264]	1[265]
23	[Inflammatory]	**Hypertension**	92,799,900 [266]	223%[6,266]	73.6[267]	73.4[267]			.216[6]	5[1,74,268, 269,270]	3[268,269,271]	2[268,272]	2[268,273]	2[268,274]	1[275]
24	Renal	**Kidney Stones**	28,620,000 [276]	246%[277]	5.3[278]	5.275[278]	4.5[278]	0.775		1[279]	2[279,280]	1[281]	1[282]	1[283]	1[284]
25	Inflammatory	**Kidney Disease: ESRD**	871,000[285]	413%[285]	32.0[286]	32[286]	32[286]			2[74,287]	1[287]	1[288]	1[289]	1[290]	1[291]
26	[Inflammatory] [292,293]	**Leukemia**	327,520[294]	588%[294]						1[295]	1[296]	1[297]	1[298]	1[299]	1[300]
27	Autoimmune/ Neurological/ Inflammatory	**Lupus (SLE)**	563,542[301]	787%[6,282]	9.9[302]	9.77[302]	5.8[302]	3.97[302]	.099[6]	3[1,74,108]	2[75,108]	1[303]	1[304]	1[305]	1[117]
28	Inflammatory [306,307]	**Melanoma**	996,587[308]	145%[308]	3.349[309]	3.349[309]	3.349[309]			2[74,310]	1[310]	1[311]	1[312]	1[311]	1[313]
29	Autoimmune [224]/ Inflammatory	**Multiple Sclerosis**	2,100,000[314]	117%[6,314]	10.1[315]	10[315]	10[315]		.102[6]	7[146,47, 74,107,111, 316,317]	6[46, 47,107,111,31 6,317]	1[47,318]	4[107, ,317,319, 320]	2[47,321, 322]	1[323]
30	Metabolic	**Obesity**	110,736,980 [324]	260%[6,325, 326]	215.9[6,327]	215[327]	161.3[327]		.857[6]	1[328]	2[328,329]	1[330]	2[220,331]	1[332]	1[333]
31	Mental Health/ Neurological	**Psychosocial: Attentional Problems**		819%[334]						1[10]	1[10]	3[10,11,12]	1[13]	1[14]	1[15]
32	Mental Health/ Inflammatory	**Psychosocial: Emotional Problems**		2500%[334]						5[98,99,100 ,101,102]	4[98,99,100,1 01]	4[98,99,10 0,103]	4[98,99,10 0,103]	3[98,100,1 03]	1[104]
33		**SLEEP complaints and Disorders**	100,825,520 [††335]		164.133[†† 6,336]	163.9[†† 336]	13.9[†† 336]	150[†† 337]	.233[6]	3[338,339, 340]	6[329,338,339 ,340,341,342]	5[340,341, 343,344, 345,	6[341,344, 346,347, 348,349]	3[340,350, 351,	3[352,353, 354]

[††] We use 40% assumption from this study against 2017 adult population statistics. We use only statistics for *Sleep Disturbances* for "total affected" and "costs." While totals for Sleep Apnea and Insomnia combine for $533 Billon, which is $359 B more than Sleep Disturbances alone, we've adopted the $164 B total for Sleep to cover all categories of sleep tracked. Men at 22%; women at 17% of adult population: 252,063,800 (2017).

	Category	Disease/ Condition	Total Affected	Generation Growth Rate	Total Cost	Economic burden ($B)	Direct/ Care Cost ($B)	Indirect/ Lost Prod	Research ($B)	Peroxynitrite	NOX-Tyrosine Nitration	OX	CI	MD	AD
34	Neurological[355]	**Sleep Apnea**	[50,160,693] ††[336,356]	430%[336, 356]	[420] ††[336, 357]	[420] ††[336, 357]	[115] ††336	[305] ††357		1[339]	4[329,341,342,339]	2[341, 344]	3[341, 344,348]	1[350]	1[358]
35		**Sleep: Dissatisfaction**	[43,370,400] †† 359	165%[359]						1[340]	1[340]	1[340]	2[346,347]	1[350]	1[354]
36	[Neurological] [360]	**Sleep: Insomnia**	[48,396,250] †† 361	123%[361]	[113.9] ††336	[113.9] ††336		100†† 336		1[340]	1[340]	1[340]	1[349]	1[340]	1[354]
37	[Inflammatory] [362,363]	**Squamous Cell Cancer**	322,762[364]	177%[364]						2[74,365]	3[365,366,367]	1[368]	1[369]	1[370]	1[371]
38	Neurological	**Stroke**	6,800,000[372]	262%[372] (age 20-54)	34.3[6,373, 374]	34.3[373,374]	34[373,374]		.300[6]	2[1,47, 74,209,375]	1[47,375]	1[47,376]	1[377]	1[47,378]	1[379]
39	Metabolic[380]/ Inflammatory	**Thyroid Dysfunction**	20,000,000 [381]	233%[381]	4.3[382,383]	4.3[382,383]	4.3[382,383]			1[384]	1[384]	1[385]	1[386]	1[387]	1[388]
40	Metabolic[380]/ Inflammatory/ [Autoimmune[2-24]]	**Hypothyroidism**	Incl. above	702%[389]						1[384]	1[384]	1[385]	1[386]	1[387]	1[388]
	All Diseases		**Total Affected**	**AVG Generation Growth Rate**	**TOTAL COSTS ($B)**	**Total Economic Burden ($B)**	**Care Cost ($B)**	**Lost Productivity/ Indirect Costs ($B)**	**Research ($B)**						
			682,024,027		**$2,777.69**	**$2,503**	**$1,276**	**$1,227 (estimate)**	**$5.36**						

361- 19.2% adults in 2012, using 2017 population statistics.

Note: In compiling the data for this paper, we reviewed 190 diseases and chronic conditions, most of which have shown steady growth in the past twenty-five years. We chose the forty chronic diseases based on the metric of doubling in prevalence over the course of a generation.

Appendix: Sample biological impacts of peroxynitrite:

Excerpts from "Nitric Oxide and Peroxynitrite in Health and Disease." (Some citations included in this paper will reflect numbering systems of both papers).

NITRATIVE STRESS

- **Creates nitrative stress:** peroxynitrite readily yields nitrotyrosine in yields of 3–14%. Nitrosative stress produces products such as nitrosothiols and nitrosamines, but nitrotyrosine and nitrotryptophan are more stable products and indicative of a *more intense oxidative stress.* This stress is better characterized as *nitrative stress*[1].
- **Tyrosine nitration**: represents a major cytotoxic pathway in the nervous system, possibly contributing to neurodegenerative disorders. Mitochondria are particularly vulnerable targets of oxidative stress and protein nitration in neurodegeneration (1135). [390]
    - Myeloperoxidase reacts rapidly and directly with peroxynitrite to produce nitrogen dioxide and efficiently catalyzes tyrosine nitration (**400**, **1112**). [391,392]
    - When peroxynitrite acts as an oxidant, it produces nitrite and hydroxide ion rather than isomerizing to nitrate. Consequently, the major decomposition products of superoxide and peroxynitrite formation in the phagosome are ultimately hydrogen peroxide and nitrite. These are also substrates for myeloperoxidase and can be a significant source of tyrosine nitration (**158**,**668**, **1113**) [393,394,395]
    - It will be the rare exception to find nitrotyrosine being formed without peroxynitrite being a major intermediate.
    - Tyrosine nitration has been identified in at least 50 human diseases and more than 80 conditions modeled in animals, as reviewed recently (**476**),[74] and these figures are continuously increasing.
- **Peroxynitrite damages complex I in the mitochondria** (**919**, **1062**) [396,397]and might further amplify injury. One of the major consequences of peroxynitrite production within mitochondria is nitration and inactivation of mitochondrial Mn-SOD (**826**, **827**, **830**). [398,399,400]
- **Nitration of tyrosine**: In most reported studies, nitration of tyrosine has been associated with a significant loss of function of the nitrated protein. An important example of loss of enzyme activity is that of mitochondrial Mn-SOD, which was the first protein found to be nitrated in vivo. Nitration of a single tyrosine residue (Tyr-34) leads to complete enzyme inactivation (**830**)[400], with the possible consequence to favor peroxynitrite generation in this organelle, due to the impaired dismutation of $O_2^{\bullet-}$. In vivo, nitration of Mn-SOD has been detected in rodent (**828**)[401] and human (**826**)[398] rejected kidney allographs, in cerebrospinal fluid of patients with amyotrophic lateral sclerosis as well as Alzheimer's and Parkinson's diseases (**27**),[402]and in hearts from humans with diabetes (**1397**)[403] and from mice exposed to cigarette smoke (**691**)[404], and it has also been associated with vascular aging (**1311**)[405].
- **Peroxynitrite nitrates and inhibits Mn-SOD** (**830**) [400], thereby preventing the breakdown of locally produced superoxide, which further fuels the formation of peroxynitrite.
- **Tyrosine nitration** affects protein structure and function, resulting in the generation of antigenic epitopes, changes in the catalytic activity of enzymes, altered cytoskeletal organization, and impaired cell signal transduction (**1132**)[406], and is thus increasingly considered as a central aspect of peroxynitrite-mediated cytotoxicity.
- **In vivo, nitration of Mn-SOD has been detected** in cerebrospinal fluid of patients with ALS, Alzheimer's disease, and Parkinson's disease (**27**)[402].

- **Tyrosine Nitration and the heart**: In the heart, nitration of several critical proteins has been proposed as a major mechanism of cardiac dysfunction (**995**, **1300**)[407,408]. Thus both creatine kinase (**740**[409], **877**[410], **878**[411], **883**[412]), a critical energetic controller of cardiomyocyte contractility, and the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2A) (**789**[413], **1397**[403]) are rapidly inactivated by tyrosine nitration. Peroxynitrite also nitrates and inactivates the voltage-gated K^+ channels in the coronary endothelium, which may foster cardiac dysfunction by imparing coronary flow reserve (**754**)[414], and nitrates several important structural protein in cardiomyocytes such as desmin, myosin heavy chain, and α-a
- **Tyrosine Nitration and Neurodegenerative Diseases such as Parkinson's**: Tyrosine nitration represents a major cytotoxic pathway in the nervous system, possibly contributing to neurodegenerative disorders. α-Synuclein, a neuronal presynaptic protein, undergoes oligomerization upon peroxynitrite-mediated nitration, forming Lewy bodies, the hallmark of Parkinson's disease (**22**)[415], and nitrated α-synuclein has been detected both in experimental and human Parkinson's disease (**443**, **1042**)[416,417].
- **Tyrosine Nitration and Dopamine**: Peroxynitrite further contributes to Parkinson's disease through nitration (and cysteine oxidation) of tyrosine-hydroxylase, the rate-limiting enzyme in the synthesis of dopamine (**103**, **720**, **721**, **1005**). [418,419,420,421]
- **Tyrosine Nitration : Neurological Diseases: Alzheimer's and ALS:** Peroxynitrite nitrates the microtubule-associated tau protein, inducing tau aggregation, a critical mechanism of Alzheimer's disease (**1073**, **1074**)[40,422], while peroxynitrite-mediated nitration of neurofilament L may be involved in the alterations of motor neurons in amyotrophic lateral sclerosis (**247**).[423]
- **Peroxynitrite disabling of several cytoskeletal proteins** by nitration represents a further major cytotoxic effect attributed to peroxynitrite. Tubulin nitration by peroxynitrite or by direct incorporation of free nitrotyrosine has been reported in cell lines derived from intestine (**54**),[424] neurons (**1269**),[425] and muscle (**199**),[426] resulting in the loss of normal physiological functions
- **Peroxynitrite disorganizes actin polymerization through actin nitration**, and via the nitration of profilin (**658**,**659**),[427,428] an important actin-binding protein. These effects have been associated with platelet dysfunction (**659**),[428] disruption of both intestinal (**55**) and endothelial barrier function (**940**),[429] as well as impaired migration and phagocytosis of activated polymorphonuclear cells (**221**).[430]
- **High concentrations of peroxynitrite enhance nitrotyrosine formation** (which is generally not reversible) and downregulates phosphotyrosine signaling, suggestive of a direct competition between nitration and phosphorylation of tyrosine at high peroxynitrite concentrations. (839)[431]

OXIDATIVE STRESS

- **Produces hydroxyl radical**: Beckman et al. (75) [432] showed peroxynitrite was a far more effective means of producing hydroxyl radical than the widely accepted reaction of reduced iron with hydrogen peroxide (known as the Fenton reaction or the iron-catalyzed Haber-Weiss reaction). These results were confirmed by Hogg et al. using systems to cogenerate superoxide and NO (287, 559). [433,434]
- **Produces Nitrogen Dioxide** → produces oxidation products like those found in cigarettes and air pollution: peroxynitrite produced nitrogen dioxide, which could lead to novel oxidation products that were previously only suspected to occur after exposure to cigarette smoke or to air pollution.

- **Acts as a strong oxidant:** Peroxynitrite itself is also a strong oxidant and can react directly with electron-rich groups, such as sulfhydryls (1056) [435], iron-sulfur centers (182), [436] zinc-thiolates (245), [437] and the active site sulfhydryl in tyrosine phosphatases (1254). [438]
- **Peroxynitrite oxidizes glutathione**. In addition to protein-bound thiol, peroxynitrite can directly oxidize low-molecular-weight thiols, most notably reduced glutathione (GSH). GSH thereby serves as an efficient endogenous scavenger of peroxynitrite and plays a major role in the cellular defense against this species (**31**).[439] Accordingly, the susceptibility of cells to peroxynitrite toxicity largely depends on the amount of intracellular GSH. GSH depletion enhances peroxynitrite toxicity and tissue injury during circulatory shock (**258**,**278**),[440,441] and a relationship between GSH depletion and enhanced peroxynitrite toxicity has also been proposed as contributing to the development of some neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis (**847**, **1321**).[442,443]
- **Combines with CO2 to create toxic carbonate radical**. The direct reaction of peroxynitrite with CO_2 ($4.6 \times 10^4\ M^{-1} \cdot s^{-1}$ at 37°C) gives rise to an unstable product (nitrosoperoxycarbonate, $ONOOCO_2^-$), which rapidly homolyzes into the $CO_3^- \cdot$ (carbonate radical) and $NO_2 \cdot$ (**34**).[444] Carbonate radical is likely to be more toxic than hydroxyl radical and yields many of the same types of oxidation commonly attributed to hydroxyl radical. Thus carbon dioxide redirects much of the peroxynitrite produced in vivo towards radical mechanisms (**16**).[445]
- **Reacts with carbon dioxide to create the *carbonate radical*;** a significant biological oxidant**.** Carbon dioxide reacts with peroxynitrite to form a transient intermediate nitrosoperoxycarbonate that rapidly decomposes homolytically to nitrogen dioxide and carbonate radical. Carbonate radical is more selective than hydroxyl radical but will initiate many of the damaging reactions commonly attributed to hydroxyl radical in the biological literature and is perhaps more significant as a biological oxidant (873).[446]
- **Peroxynitrite exacerbates oxidative damage to mitochondrial proteins.** Peroxynitrite targets cytochrome *c*, the nitration of which significantly impairs its redox properties. Notably, cytochrome *c* nitration increases its peroxidatic activity, leading to the generation of hydrogen peroxide and exacerbation of oxidative damage to mitochondrial proteins (**178**, **627**).[447,448]
- **Peroxynitrite may alter protein structure and function** by reacting with various amino acids in the peptide chain. The most prevalent reaction is that with cysteine, making thiol oxidation a major modification introduced by peroxynitrite (**1056**, **1057**).[435,449] The direct second-order reaction of peroxynitrite with thiols (particularly with the anion form, RS^-) results in the formation of an intermediate sulfenic acid (RSOH), which then reacts with another thiol, forming a disulfide (RSSR) (**16**).[445] Thiols may also be oxidized by the radicals formed from peroxynitrite, generating thiyl radicals (RS·). Thiyl radicals may react with oxygen and promote oxidative stress by propagating free radical reactions (**334**).[450] They will also react with NO to form nitrosothiols.
- **Modifies proteins** containing a heme prosthetic group, such as hemoglobin (106) [451], myoglobin (540) [452], or cytochrome *c* (1275) [453], oxidizing ferrous heme into the corresponding ferric forms.
- **Neurodegenerative: Alzheimer's. Peroxynitrite directly oxidizes methionine**, forming methionine sulfoxide, and to a lesser extent, ethylene and dimethyldisulfide (**16**).[445] These modifications may participate in immune defenses by inactivating glutamine synthetase (**90**)[454] and the molecular chaperone GroEL (**673**)[455] in bacteria. Met oxidation also inhibits α1-antiproteinase, which then loses its ability to inactivate proteases, most notably elastase (**1368**).[456] Methionine oxidation is reversed by methionine sulfoxide reductase, an enzyme

whose reduced expression in the brain is associated with the development of Alzheimer's disease (**1199**).[457]

- **Peroxynitrite can also oxidize tryptophan** (**16**),[445] yielding *N*-formylkynurenine, oxindole, hydropyrroloindole, and nitrotryptophan,
- **Peroxynitrite modifies histidine**, which inactivates copper and **oxidize tryptophan**. (through a radical mechanism, forming a histidinyl radical, a mechanism involved in the inactivation of Cu,Zn-SOD by peroxynitrite (**15**, **1403**, **1404**).[458,459,460]

MITOCHONDRIAL DYSFUNCTION

Mitochondria are involved in many vital processes, e.g., energy production, calcium homeostasis, and the control of various biosynthetic pathways. They also play essential roles in cell death mechanisms. Disruption of mitochondrial functions is implicated in a great number of disease processes, such as diabetes, atherosclerosis, ischemic heart diseases, stroke, aging, and neurodegenerative diseases.

Peroxynitrite may affect every critical function of the Mitochondria. The pivotal role of peroxynitrite in such derangements is increasingly recognized, as it can react with key components of mitochondria and thus may affect virtually every critical function of these organelles.

- **Peroxynitrite formation in Mitochondria**. Mitochondria can produce both NO, by the activity of a Ca^{2+}-sensitive mitochondrial NOS (mtNOS) (**140**, **528**), and superoxide, following the partial reduction of oxygen within the mitochondrial matrix due to the natural leak of electron from the respiratory chain.
- **Interruption of electron transfer at cytochrome oxidase increases the leakage of electrons leading to enhanced formation of superoxide within the mitochondrial matrix and generation of peroxynitrite**. A major physiological function of NO in the mitochondria is to regulate oxygen consumption by reversibly inhibiting cytochrome-*c* oxidase (complex IV of the electron transport chain) via competition with oxygen for the binuclear binding site (**1001**). In conditions of high NO production (e.g., during inflammation, reperfusion injury, or neuronal hyperactivation), the interruption of electron transfer at cytochrome oxidase markedly increases the leakage of electrons from the respiratory chain, resulting in enhanced formation of superoxide within the mitochondrial matrix and generation of significant amounts of peroxynitrite (**143**, **147**, **533**).
- **Peroxynitrite nitrates and inhibits Mn-SOD** (**830**), thereby preventing the breakdown of locally produced superoxide, which further fuels the formation of peroxynitrite.
- **Mitochondrial toxicity of peroxynitrite** results both from direct oxidative reactions and from free radical-mediated damage (**1058**, **1059**), secondary to peroxynitrite reacting with CO_2, giving rise to $CO_3^{-}\cdot$ and $NO_2\cdot$ radicals. The latter reaction is particularly favored within mitochondria, which are the main organelles where CO_2 is produced during decarboxylation reactions (**1058**, **1059**).
- **Peroxynitrite inactivation of Mn-SOD triggers cardiac failure and CNS pathology that includes mitochondrial vacuolization and oxidized lipid deposits**. Serious consequences arise from the genetic knockout of Mn-SOD, which is generally lethal in the neonatal period. In addition to causing cardiac failure, the mitochondrial Mn-SOD knockout mouse suffers CNS pathology that includes mitochondrial vacuolization and oxidized lipid deposits. Conversely, genetically induced increased expression of mitochondrial Mn-SOD or induction of the enzyme during stress has been shown to protect mitochondria and cells from oxidative stress. The inactivation of Mn-SOD by peroxynitrite will make mitochondria more vulnerable in neurodegeneration

- **Peroxynitrite damages complex I in the mitochondria** (**919**, **1062**)[396,397] and might further amplify injury. One of the major consequences of peroxynitrite production within mitochondria is nitration and inactivation of mitochondrial Mn-SOD (**826**, **827**, **830**). [398]
- **Peroxynitrite exerts significant inhibition to most components of the electron transport chain,** including complex I (NADH dehydrogenase) (**146**, **919**, **1016**) [396], complex II (succinate dehydrogenase) (**111**,**1092**), complex III (cytochrome *c* reductase) (**489**, **1016**), and complex V (ATP synthetase) (**177**,**1058**, **1059**), through mechanisms involving, to various extents, cysteine oxidation, tyrosine nitration, and damage of iron sulfur centers, as extensively reviewed in References **1058** and**1059**
- **Peroxynitrite exacerbates oxidative damage to mitochondrial proteins.** Peroxynitrite targets cytochrome *c*, the nitration of which significantly impairs its redox properties. Notably, cytochrome *c* nitration increases its peroxidatic activity, leading to the generation of hydrogen peroxide and exacerbation of oxidative damage to mitochondrial proteins (**178**, **627**).
- **Permeability transition pore (PTP) induces mitochondrial swelling and rupture of the outer membrane** with subsequent efflux of proapoptotic molecules. Depending on the degree of MPT, cells may either recover (minimal MPT) or die by apoptosis (moderate or transient MPT, with maintained ATP production) or necrosis (widespread and irreversible MPT, leading to severe ATP depletion) (**982**,**984**, **1356**).
- **Increased superoxide production in mitochondria** should render them vulnerable when exposed to NO (**532**)[47]
- **Peroxynitrite impairs energy metabolism** by inhibiting the tricarboxylic acid cycle enzyme aconitase, located in the mitochondrial matrix, via oxidative disruption of the 4Fe-4S center of the enzyme (**182**, **511**), as well as mitochondrial creatine kinase, which is present in the intermembrane space (**1197**).
- **Peroxynitrite oxidizes Nicotinamide nucleotide transhydrogenase, which allows formation of NADPH** from NADH and NADP. This mitochondrial protein is oxidized, nitrated, and inactivated by peroxynitrite (**403**). The ensuing depletion of NADPH reduces the mitochondrial ability to regenerate GSH, contributing to the amplification of oxidative stress within the organelle.

INFLAMMATION

- **Activates NFκB and stimulates interleukin (IL**). –a series of elegant studies from Janos Filep's group in Montreal have shown that peroxynitrite, both exogenously added or endogenously produced in response to LPS, cytokines, or Toll-receptor 9 stimulation, potently activated NFκB and stimulated thereby interleukin (IL)-8 secretion by human polymorphonuclear cells (**391**, **640**, **674**, **1476**). [461,462,463,464] These studies thus identified an important signaling mechanism by which peroxynitrite amplifies neutrophil-dependent responses under inflammatory conditions. Matata et al. (**851**) [465] also reported that mononuclear cells exposed to micromolar concentrations of peroxynitrite disclosed NFκB activation and a stimulated production of TNF-α and IL-6. These authors proposed that nitration of tyrosine-42 in IκB might increase its degradation, triggering NFκB activity (**851**)[465].
- **Inflammatory Disease: Demyelination**: Peroxynitrite may play a critical role in inflammatory diseases of the nervous system by initiating peroxidation of myelin lipids, leading to demyelination (**1155**,**1175**, **1313**).
- **Peroxynitrite activates NFκB** A series of elegant studies from Janos Filep's group in Montreal have shown that peroxynitrite, both exogenously added or endogenously produced in response

to LPS, cytokines, or Toll-receptor 9 stimulation, potently activated NFκB and stimulated thereby interleukin (IL)-8 secretion by human polymorphonuclear cells (391, 640, 674, 1476). These studies thus identified an important signaling mechanism by which peroxynitrite amplifies neutrophil-dependent responses under inflammatory conditions.

- Matata et al. (851) [465] also reported that mononuclear cells exposed to micromolar concentrations of peroxynitrite disclosed NFκB activation and a stimulated production of TNF-α and IL-6. These authors proposed that nitration of tyrosine-42 in IκB might increase its degradation, triggering NFκB activity (851). [465]
- **Enhances inflammatory cell recruitment**
- **Peroxynitrite activation of proinflammatory cytokines activates nitric oxide.** Enhanced NO production due to induced expression of iNOS by proinflammatory cytokines is instrumental in the pathophysiology of inflammation**.**

IMMUNITY

- **Negatively affects normal immune response**: the impairment of tyrosine phosphorylation by peroxynitrite may affect various fundamental cellular functions. For example, in T lymphocytes, peroxynitrite triggered widespread protein nitration and blocked tyrosine phosphorylation in response to cell activation through the T-cell receptor (TCR)/CD3 complex. This resulted in a depressed proliferative response of activated T cells, suggesting that peroxynitrite might negatively affect normal immune responses depending on T cells in vivo.
- **Autoimmune: Lupus, arthritis and glomerulonephritis:** the modulation of tyrosine kinase-dependent signaling, peroxynitrite and cell signaling, and the generation of new epitopes on proteins, to which T and B lymphocytes are not rendered tolerant. A number of nitrotyrosine-carrying proteins have thus been shown to elicit both humoral and cellular immune responses in mice (102, 966), and recent findings indicate that nitrated proteins may be involved in the development of autoimmune diseases such as systemic lupus erythematosus, arthritis, and glomerulonephritis (571, 671).
- **The impairment of tyrosine phosphorylation by peroxynitrite may affect various fundamental cellular functions**. For example, in T lymphocytes, peroxynitrite triggered widespread protein nitration and blocked tyrosine phosphorylation in response to cell activation through the T-cell receptor (TCR)/CD3 complex. This resulted in a depressed proliferative response of activated T cells, suggesting that peroxynitrite might negatively affect normal immune responses depending on T cells in vivo (137).

DNA DAMAGE

- Peroxynitrite can damage DNA by introducing oxidative modifications in both nucleobases and sugar-phosphate backbone (for review, see Refs. 160, 945). Among the four nucleobases, guanine is the most reactive with peroxynitrite due to its low reduction potential (1422). The major product of guanine oxidation is 8-oxoguanine, which further reacts with peroxynitrite, yielding cyanuric acid and oxazolone (945). Ultimately, guanine oxidation by peroxynitrite results in guanine fragmentation, a critical step towards mutagenesis and carcinogenesis (160, 945).
- **Peroxynitrite can nitrate guanine**, yielding 8-nitro-guanine, which leads to the formation of abasic sites that can be cleaved by endonucleases in vivo to give DNA single-strand breaks (160, 945,1422).

- **The formation of DNA single-strand breaks** represents a critical aspect of peroxynitrite-mediated cytotoxicity, since they represent the obligatory trigger for the activation of the nuclear enzyme poly(ADP-ribose) polymerase (PARP) (**1243**), a pathway ultimately related to the induction of cell death and tissue inflammation, as developed in detail in the next section.

ENDOTHELIAL DYSFUNCTION

- **Prostacyclin synthase (PGI_2 synthase) is another important target of peroxynitrite** that is inactivated by a specific nitration of Tyr-430 (**1130**). PGI_2 synthase is rapidly nitrated in arterial walls during inflammatory processes (**39**), through a mechanism involving CD40 ligand-dependent increases in vascular peroxynitrite generation (**290**). The consecutive loss of PGI_2 synthesis may be a significant contributor to endothelial dysfunction in many pathological conditions, e.g., diabetes (**1473**), atherosclerosis (**290**), and ischemia-reperfusion (**1468**) and may play an important role in the phenomenon of nitrate tolerance (**549**).

INACTIVATES ENZYMES

- **The oxidation of critical cysteine residues by peroxynitrite inactivates many enzymes** involved in cellular energetic processes, including glyceraldehyde-3-phosphate deshydrogenase (**157**, **1192**), creatine kinase (**703**), complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), and complex III (cytochrome *c* reductase) as well as complex V (ATP synthase) from the mitochondrial respiratory chain (**1058**, **1059**, **1062**). [397]
- **Cysteine oxidation by peroxynitrite may result in enzyme activation** instead of inhibition, as demonstrated for matrix metalloproteinases (MMPs), which have been recently implicated as an important mechanism of peroxynitrite-dependent toxicity in heart disease (**994**,**1085**, **1345**) and stroke (**495**).

EPITHELIAL DAMAGE

- **Causes airway hyperresponsiveness and airway epithelial damage**. .
- **Inhibits pulmonary surfactant.** Asthma is characterized by increased airway hyperresponsiveness, airway epithelial shedding, and inflammation. (2) [466]

NEUROTRANSMITTER DISRUPTIONS

- **Tyrosine Nitration and Dopamine**: Peroxynitrite further contributes to Parkinson's disease through nitration (and cysteine oxidation) of tyrosine-hydroxylase, the rate-limiting enzyme in the synthesis of dopamine (**103**, **720**, **721**, **1005**).

LIPID PEROXIDATION

- **Lipid Peroxidation**: A major aspect of peroxynitrite-dependent cytotoxicity relies on its ability to trigger lipid peroxidation in membranes (**1055**), liposomes, and lipoproteins by abstracting a hydrogen atom from polyunsatturated fatty acids (PUFA). Resulting products include lipid hydroperoxyradicals, conjugated dienes, and aldehydes (**311**). Such radicals in turn attack neighboring PUFAs, generating additional radicals which propagate free radical reactions and

the degeneration of membrane lipids (560, 1055), causing membrane permeability and fluidity changes with significant biological consequences (1075).

- **Oxidizing agent toward LDL leading to atherogenesis.** Peroxynitrite acts as a potent oxidizing agent towards low-density lipoprotein (LDL) (742,1287). Peroxynitrite-modified LDL binds with high affinity to scavenger receptors leading to the accumulation of oxidized cholesteryl esters and foam cell formation, which represent a key early event in atherogenesis (465, 498, 558).
- **Secondary oxidative insults:** peroxynitrite with membrane lipids may lead to the formation of various nitrated lipids, with potential biological properties as mediators of signal transduction both under physiological and pathological conditions (50), and of several intermediates products, including isoprostanes and 4-hydroxynonenal that can further trigger secondary oxidative insults (311)

APOPTOSIS

Once the level of cellular damage inflicted by peroxynitrite supersedes any possibility of repair, the cell eventually dies via one of the two main pathways of cell demise, necrosis or apoptosis. Necrosis is associated with loss of cellular ATP, leading to membrane disruption, release of noxious cellular debris, and the development of secondary inflammation. In contrast, apoptosis occurs in a well-choreographed sequence of morphological events characterized by nuclear and cytoplasmic condensation with blebbing of the plasma membrane. The dying cell eventually breaks up into membrane-enclosed particles termed apoptotic bodies, which are rapidly ingested and degraded by professional phagocytes or neighboring cells, without inducing any inflammatory response.

- **Cell Death: Apoptosis from cell signals**: In addition to directly targeting the mitochondria, peroxynitrite can also activate cell death mechanisms through the modulation of various cell signal transduction processes. The role of mitogen-activated protein kinases (MAPKs) and Akt (protein kinase B) deserves some comment here, though more details on these cascades are given in section V. MAPKs comprise three distinct members, ERK, JNK, and p38, whose activation regulates many critical cellular functions, notably apoptosis, and which are strongly activated by peroxynitrite in vitro

- **Peroxynitrite mediated apoptosis across cell types:** in HL-60 cells (773), PC12 cells (367), fibroblasts (1064), SN 4741 dopaminergic neurons (1148), SH-SY5Y neuroblastoma cells (1101), primary neurons (115, 370, 664, 665), astrocytes (1452) and oligodendrocytes (1439), endothelial cells (319, 1339), beta islet cells (309, 1210), neutrophils (408, 1267), chondrocytes (1366), cardiomyocytes (30, 750), and renal tubular cells (13).
- **Peroxynitrite acts via mitochondrial permeability transition (MPT**) (29), which is a prominent feature of peroxynitrite-mediated cell death. MPT describes the permeabilization of the inner mitochondrial membrane by a multiprotein complex termed the permeability transition pore, which is composed of the adenine nucleotide translocase (ANT), cyclophilin D (CyP-D) and the voltage-dependent anion channel (VDAC). Formation of the permeability transition pore is triggered by calcium overload or by oxidative modifications of critical thiol groups within the ANT, allowing its interaction with CyP-D. The permeability transition pore results in the dissipation of mitochondrial membrane potential ($\Delta\psi_m$), cessation of electron transfer and ATP production, and the secondary production of reactive oxygen species within the mitochondria, which further amplify the phenomenon.
- **Permeability transition pore (PTP) induces mitochondrial swelling and rupture of the outer membrane** with subsequent efflux of proapoptotic molecules. Depending on the degree of MPT,

cells may either recover (minimal MPT) or die by apoptosis (moderate or transient MPT, with maintained ATP production) or necrosis (widespread and irreversible MPT, leading to severe ATP depletion) (**982**,**984**, **1356**).

- **Permeability transition pore (PTP) opening in response to peroxynitrite** has been documented in isolated mitochondria (**118**, **142**, **1127**, **1326**), where it is likely to occur as a consequence of peroxynitrite-mediated oxidation of cysteine-bound thiols in the ANT (**1326**).
- **Calcium overload enhances PTP opening by peroxynitrite** suggest that calcium-dependent sensitization of certain mitochondrial proteins to oxidative/nitrative damage is critical for apoptosis to proceed following peroxynitrite exposure (**142**).
- **Peroxynitrite causes dissipation of mitochondrial potential** (**216**, **758**, **1148**, **1332**, **1339**), **mitochondrial efflux of cytochrome** *c* (**758**, **1339**), and **caspase activation** (**1148**, **1339**) occurred to various extents in different cells exposed to endogenously produced or exogenously added peroxynitrite

CELL SIGNALING and PEROXYNITRITE

The concept of cell signaling defines the ability of cells to detect changes in their environment to generate an appropriate physiological response (**1362**). In the past few years, significant experimental efforts have been put forward to explore the relationships between cellular oxidative processes and the modulation of cell signal transduction, collectively grouped under the concept of "redox signaling" (**848**). The early observation that NO could regulate many critical cell signaling processes through *S*-nitrosylation of critical cysteine residues in proteins was a milestone discovery in our understanding of redox regulation of signal transduction (**1200**). Soon thereafter, the identification of peroxynitrite's ability to nitrate tyrosine residues rapidly focused attention on phosphorylation cascades, as this protein modification was found to inhibit cell signaling processes relying on tyrosine phosphorylation. Although this view was initially strongly considered, it proved to be overly simplistic, as peroxynitrite often promoted phosphotyrosine signaling in many instances. Further evidence was gathered that, in many different cell systems in vitro, peroxynitrite behaved as a potent modulator of an array of cell signal transduction pathways, independently from its ability to nitrate tyrosine. After a brief summary of the main cell signal transduction pathways, these emerging aspects of peroxynitrite biology are discussed in detail.

Most extracellular signals are sensed by two major families of cell membrane receptors, G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (**1362**). GPCRs interact with G proteins (guanine nucleotide binding proteins), which act on several downstream effectors to generate second messengers such as inositol trisphosphate, cyclic nucleotides, or Ca^{2+}, which in turn modulate the degree of protein phosphorylation. GPCRs also activate small G proteins (Ras and Rho families) that lie upstream of the MAPK superfamily of proteins (see below) (for review, see Refs. **98**, **497**). Receptor tyrosine kinases (RTKs) are transmembrane glycoproteins consisting of at least 13 families, e.g., receptors for insulin and growth factors. Upon binding by specific ligands, RTKs create docking sites for specific phosphotyrosine binding domains to recruit and activate downstream effectors, including Ras-MAPKs, phosphatidylinositol 3-kinase (PI3K), and protein kinase C. RTKs control most fundamental cellular processes such as cell proliferation, differentiation, and cell survival, and abnormal RTK-dependent signaling has been linked to a number of disease processes, notably cancer and cardiovascular diseases (for review, see Refs.**577**, **1129**).

MODULATION of CELL SIGNALING by PEROXYNITRITE

- **Peroxynitrite induced nitration tyrosine residues can impair signaling processes** depending on tyrosine phosphorylation. Early in vitro studies using peptide substrates showed that phosphorylation of critical tyrosine residues within these peptides was markedly inhibited by peroxynitrite-mediated tyrosine nitration (**463**, **702**), and further results indicated that tyrosine nitration blocked downstream signaling in intact cell systems in vitro
- In the human neuroblastoma SH-SY5Y cells, the **peroxynitrite generator SIN-1 triggered the nitration of the focal adhesion protein p130^{cas}, resulting in the blockade** of its phosphorylation and interfered with the assembly of focal adhesion complexes (**1100**).

- **Peroxynitrite-dependent nitration of a key tyrosine residue (Tyr686) interferes with its phosphorylation and prevents binding to the protein-tyrosine phosphatase SHP-2.** Nitration of tyrosine residue (Tyr686) within the cytoplasmic domain of the adhesion molec interferes with its phosphorylation by src family protein kinases, and prevents its binding to the protein-tyrosine phosphatase SHP-2 ule platelet-endothelial cell adhesion molecule-1 (PECAM-1), interferes with its phosphorylation by src family protein kinases, and prevents its binding to the protein-tyrosine phosphatase SHP-2 (**941**).

- **The impairment of tyrosine phosphorylation by peroxynitrite may affect various fundamental cellular functions**. For example, in T lymphocytes, peroxynitrite triggered widespread protein nitration and blocked tyrosine phosphorylation in response to cell activation through the T-cell receptor (TCR)/CD3 complex. This resulted in a depressed proliferative response of activated T cells, suggesting that peroxynitrite might negatively affect normal immune responses depending on T cells in vivo (**137**).

- **Nitrotyrosine disrupts complex chain of signal transduction**. Nitrotyrosine formation in human platelets inhibited tyrosine phosphorylation in response to thrombin, thereby preventing their activation (**795**, **896**) [467,468]. Under certain conditions, competition between nitration and phosphorylation on a single tyrosine residue may completely disrupt a complex chain of signal transduction, as recently shown in primary rat hepatocytes. These cells undergo apoptotic cell death upon stimulation with CD95 (Fas) ligand. Activated CD95 then promotes the formation of a death-inducing signal complex (DISC), committing the cell to apoptosis.

- **Irreversible inhibition of PTPs by very low concentrations of peroxynitrite** has been demonstrated both in cells (**791**, **839**) and purified enzymes (**175**, **1254**). All PTPs contain a conserved cysteine residue, which forms an intermediate phosphocysteine with the phosphatase substrate of the PTP, and oxidation of this critical cysteine has been shown to inactivate the PTPs (**1254**). Peroxynitrite anion is structurally similar to phosphate anion, so that the extreme vulnerability of PTPs to peroxynitrite-mediated inactivation is consistent with attraction of peroxynitrite to the active site of the enzyme and subsequent oxidation of this essential cysteine (**1254**).
- **Peroxynitrite targets NRTK family member Src,** as a preferential target of peroxynitrite. Src family members participate in a variety of signaling processes, including mitogenesis, T- and B-cell activation, cell differentiation and proliferation, as well as cytoskeleton restructuring, through the activation of an array of downstream effectors such as PI3K, phospholipase C, and FAK (**1087**).

- In human red blood cells, the src kinase *hck* was activated by peroxynitrite via cysteine oxidation, whereas another src kinase, *lyn*, was activated through a mechanism involving the inhibition of Tyr527 binding to the SH2 domain (838, 840).

MAPK SIGNALING

- **Peroxynitrite activates MAPKS.** MAPKs (ERK, JNK, and p38) are all activated by a dual phosphorylation at a specific tripeptide motif, mediated by a conserved protein kinase cascade, involving MAP kinase kinase kinases (MKKK or MEKK) and MAP kinase kinases (MKK or MEK) (328). The upstream signaling pathways leading to MKKK activation largely depend on the activation of growth factor receptors and small G proteins, such as Ras, Rac, and Cdc42 (328, 848). Downstream targets of MAPKs include an array of proteins as well as transcription factors, whose activation regulates virtually every critical cellular function, especially apoptosis, cell proliferation, and inflammatory genes expression.

ERK PATHWAY

- **Peroxynitrite potently activates ERK**. ERK is involved in the signaling pathways triggered by growth factors and their receptors, via the successive activation of the small G protein ras, Raf-1 kinase and MEK 1 (1434). ERK can also be activated by various extracellular stresses, including oxidants and free radicals (848). In vitro, peroxynitrite potently activated ERK in fibroblasts (57, 1434), neutrophils (735, 1477), endothelial and vascular smooth muscle cells (1307), neural cells (191, 638, 645, 1099), and cardiomyocytes (1024), through strikingly distinct and cell-specific mechanisms
- **ERK activation by peroxynitrite** (up to 200 μM) has been associated with the upregulation of surface expression of the β_2-integrins CD11b/CD18 and increased neutrophil adhesion to endothelial cells (1477), as well as an enhanced oxidative burst upon stimulation (735). These data then support a potential role of peroxynitrite in mediating excessive neutrophil trafficking and superoxide generation under inflammatory conditions.
- With respect to peroxynitrite stimulation, it is noticeable that all studies performed so far have indicated a proapoptotic role of ERK. Indeed, peroxynitrite-induced apoptosis in primary rat astrocytes (1420), human SH-SY5Y neuroblastoma cells (1099), human bronchial epithelial BEAS-2B cells (922), and primary murine neurons (645) was associated with the activation of ERK and was significantly attenuated by MEK-ERK pathway inhibitors

JNK PATHWAY

- JNK exists as three distinct isoforms, activated in response to many different environmental stresses via a signaling cascade involving the small G proteins ras and rac, several MAPKKKs, MAPKK, MKK1, and MKK4, linked together by various scaffold proteins in specific signaling modules (198, 291). Activated JNK phosphorylates the protoconcogene product c-*jun*, allowing its homodimerization or heterodimerization with c-*fos* to form the active transcription factor AP-1. JNK is involved in the regulation of inflammation and cell death, with both pro- and antiapoptotic reported functions (198, 291).
- JNK activation in response to peroxynitrite has been reported in many different cell types (23,450, 922, 1024, 1128, 1162).
- Go et al. (450) showed that endogenously produced peroxynitrite was responsible for the activation of JNK triggered by laminar shear stress in endothelial cells (450).

- JNK activation by peroxynitrite was causally linked to apoptotic cell death in murine alveolar C10 cells, as cells expressing a dominant negative mutant of JNK1 were protected from peroxynitrite-mediated apoptosis (**1162**).

P38MAPK

- The p38 family consists of at least five different isoforms: α, β_1, β_2, γ, and δ, whose activation by environmental stress is controlled by several MAPKKKs as well as MKK3 and MKK6. The activation of p38 has been linked with apoptotic cell death and mitotic arrest in a great variety of cells exposed to different oxidants and free radicals (**848**).
- Peroxynitrite is extremely efficient in activating p38, as shown by the very early (within minutes) phosphorylation of p38 upon peroxynitrite stimulation, even at low concentrations (<10 μM) in cardiomyocytes (**1024**), endothelial (**350**, **450**) and vascular smooth muscle cells (**1307**), hepatocytes (**414**, **1128**), bronchial epithelial cells (**922**), and neural cells (**120**, **638**, **965**, **1120**, **1440**).

PKC pathway

- PKC represents a family of phospholipid-dependent serine/threonine kinases involved in signaling pathways regulating cell growth and differentiation, cell death, immune response, transcriptional regulation, and stress responsiveness (notably oxidative stress) (**458**, **848**). PKC-mediated cellular effects are both tissue and isoform specific. PKC exists as 11 different isoforms, subdivided in three distinct subgroups (classical PKC α, βI, βII, γ; novel PKC δ, ε, η, θ; and atypical PKC λ, ι, ζ), separated upon their particular mechanism of activation (**45**).
- **Peroxynitrite has been associated with a significant reduction of the activity of PKC α, β, ε, and ζ in neuronal cells**, and the degree of this inhibition correlated completely with the degree of tyrosine nitration within the enzyme (**689**). Importantly, PKC is essential for a number of aspects of neuronal functions including synaptic plasticity, learning, and memory. Decreased PKC activity may contribute to several neurodegenerative disorders (**66**, **689**), which are also associated with increased peroxynitrite generation (**1284**). PKC inhibition might thus represent one of the mechanisms linking peroxynitrite in the brain with neurodegeneration.

NFκB

- NFκB is a crucial transcription factor activating inflammatory and antiapoptotic genes in response to immunostimulation.
- A series of elegant studies from Janos Filep's group in Montreal have shown that peroxynitrite, both exogenously added or endogenously produced in response to LPS, cytokines, or Toll-receptor 9 stimulation, potently activated NFκB and stimulated thereby interleukin (IL)-8 secretion by human polymorphonuclear cells (**391**, **640**, **674**, **1476**). These studies thus identified an important signaling mechanism by which peroxynitrite amplifies neutrophil-dependent responses under inflammatory conditions.
- Matata et al. (**851**) [465] also reported that mononuclear cells exposed to micromolar concentrations of peroxynitrite disclosed NFκB activation and a stimulated production

of TNF-α and IL-6. These authors proposed that nitration of tyrosine-42 in IκB might increase its degradation, triggering NFκB activity (**851**). [465]

CELL SIGNAL TRANSDUCTION

- **Disrupts complex chain of signal transduction** Nitrotyrosine formation in human platelets inhibited tyrosine phosphorylation in response to thrombin, thereby preventing their activation (**795**, **896**) cross ref. Under certain conditions, competition between nitration and phosphorylation on a single tyrosine residue may completely disrupt a complex chain of signal transduction.
- **Peroxynitrite-mediated activation of ERK** committed bronchial (**922**) and neural cells (**645**, **1099**, **1420**) to apoptotic cell death,
- **Peroxynitrite mediated activation of JNK**, p38, or both triggered a similar outcome in murine alveolar cells (**1162**), cerebrocortical neurons (**120**), and PC12 cells (**1148**), respectively.
- **Peroxynitrite creates the release of free Zn^{2+}** by peroxynitrite, possibly due to oxidation of Zn^{2+}-sulfur bridges in mitochondrial and cytosolic proteins (**120**, **245**, **1469**), could play an essential role in initiating these responses (**120**, **1439**, **1440**).
- **Peroxynitrite activates MAPKs**: peroxynitrite activation of MAPKs has been associated with significant inhibition of protein kinase B (Akt), a serine-threonine protein kinase whose activation represents a powerful protective mechanism to limit apoptosis in various stress conditions, including oxidative stress (**848**).
- **Peroxynitrite blocks the activation of Akt in macrophages** (**536**), adipocytes (**949**), PC12 cells (**1148**, **1193**), and endothelial cells (**353**, **485**–**487**, **1471**), through a mechanism involving nitration and inactivation of phosphatidylinositol 3-kinase, the upstream signaling intermediate in the Akt pathway (**353**, **536**).

NECROSIS

- **High concentrations of Peroxynitrite associated with necrosis.** Whereas apoptosis is a typical consequence of low to moderate concentrations of peroxynitrite, exposure of cells to higher concentrations of the oxidant has been associated with necrosis (**115**,**1334**). Studies investigating this process have established that peroxynitrite-dependent cell necrosis is not a purely passive phenomenon, but instead is mediated by a complex process involving DNA damage and activation of the DNA repair enzyme PARP-1 (**1243**). PARP-1 is a member of the PARP enzyme family consisting of PARP-1 and many additional poly(ADP-ribosylating) enzymes. PARP-1 detects and signals DNA strand breaks induced by a variety of genotoxic insults, including ionizing radiations, alkylating agents, oxidants (essentially hydrogen peroxide, peroxynitrite, and possibly nitroxyl anion), and free radicals (mainly carbonate or hydroxyl radical) (**299**, **696**, **1230**).
- **PARP-1: peroxynitrite inducees DNA strand breakage leading to PARP activation.** An important function of PARP-1 is to allow DNA repair and cell recovery in conditions associated with a low degree of DNA damage. Upon severe DNA injury, overactivation of PARP-1 depletes the cellular stores of NAD^+, an essential cofactor of the glycolytic pathway, the tricarboxylic acid cycle, and the mitochondrial electron transport chain (**762**, **769**, **1227**, **1243**). As a result, the loss of NAD^+ leads to a marked decrease in the cellular pools of ATP, resulting in cellular dysfunction and cell death via the necrotic pathway (**503**, **765**) (**Fig. 7**). This intriguing mode of cell response to acute genotoxic stress led Berger (**86**) to propose the “suicide hypothesis” of PARP activation, which can be regarded as a way to eliminate cells after irreversible DNA injury. Evidence has

been gathered that both exogenous and endogenously generated peroxynitrite potently induce DNA strand breakage leading to PARP activation in a variety of cell types, including pulmonary (**1239**) and intestinal epithelial cells (**666**), vascular endothelial and smooth muscle cells (**430**,**1233**), fibroblasts (**1240**), macrophages (**1462**), and cardiomyocytes (**444**, **987**, **992**), to cite just a few examples.

- A vast amount of experimental studies have then established that the **PARP-1 pathway of cell death plays pivotal roles in tissue injury** and organ dysfunction in virtually every disease process accompanied by oxidative/nitrosative stress: ischemia-reperfusion, localized and systemic inflammation, diabetes, and circulatory shock to name but a few (for extensive recent reviews on this topics, see Refs.**248**, **254**, **373**, **624**, **821**, **959**, **995**, **997**, **1228**, **1245**, **1306**).
- **PARP-1 and nuclear factor kappa B (NFκB**). The second additional role of PARP-1 is its involvement in the upregulation of inflammatory processes. The absence of functional PARP-1 (either genetic or pharmacological) alleviated the expression of a host of proinflammatory mediators, including cytokines, chemokines, adhesion molecules and enzymes (e.g., iNOS, COX-2), and it also reduced tissue infiltration with activated phagocytes in experimental models of inflammation, circulatory shock, and ischemia-reperfusion (see Refs. **361**, **765**, **1230** for review). The proinflammatory function of PARP was initially believed to reflect exclusively its role as an inducer of cell necrosis, which promotes inflammation via the spilling of noxious cellular debris into neighboring tissues. However, this concept was reviewed after the demonstration by Oliver et al. (**973**) of a functional association between PARP-1 and the proinflammatory transcription factor nuclear factor kappa B (NFκB).

Results:

We tallied more than 679 million instances of disease from 36 fast-growing diseases at an annual cost to the US economy of $2.77 trillion. While these numbers are staggering, they are likely substantially understated. There are hundreds of chronic diseases and medical conditions which are not tracked in this paper. There is also limited access to current data. Few meta-studies since 2011 could be found for the diseases we tracked in this paper and economic impact data for the past 4-7 years are sparse. Thus we are left with only an impression of the actual impacts of chronic disease in America. As the growth of chronic disease is clearly both a human and economic problem, it could be valuable for US agencies to more systematically collect or sponsor acquisition of appropriate disease data. One idea is to gather more current data annually through incentives for those filing annual tax returns. Self-reported illness could provide a more vivid picture of the state of our national health.

REFERENCES:

[1] Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiol Rev. 2007 Jan;87(1):315- 424. [PubMed]
[2] Centers for Disease Control and Prevention. National Center for Health Statistics; Therapeutic Drug Use. Accessed 2016 Feb 21. [CDC]
[3] National Institute of Neurological Disorders and Stroke. Disorders A-Z; NINDS Attention Deficit-Hyperactivity Disorder Information Page. Page updated 2015 Nov 19. Accessed 2016 Feb 23. [link]
[4] Visser SN, Danielson ML, Bitsko RH, Holbrook JR, Kogan MD, Ghandour RM, Perou R, Blumberg SJ. Trends in the Parent-Report of Health Care Provider-Diagnosed and Medicated Attention-Deficit/Hyperactivity Disorder: United States, 2003–2011. J Am Acad Child Adolesc Psych; 2014 Jan; 53(1):34–46.e2. [PubMed] [link]
[5] Doshi JA, Hodgkins P, Kahle J, Sikirica V, Cangelosi MJ, Setyawan J, Erder MH, Neumann PJ. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. J Am Acad Child Adolesc Psych. 2012 Oct;51(10):990-1002.e2. [pubmed]
[6] National Institutes of Health. Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC). RePORT (Research Portfolio Online Reporting Tools); 2015 Feb 5. [link]
[7] Doshi JA, Hodgkins P, Kahle J, Sikirica V, Cangelosi MJ, Setyawan J, Erder MH, Neumann PJ. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. J Am Acad Child Adolesc Psych. 2012 Oct;51(10):990-1002.e2. [pubmed]
[8] Pelham WE, Foster EM, Robb JA. The economic impact of attention-deficit/hyperactivity disorder in children and adolescents. J Pediatr Psychol. 2007 Jul;32(6):711-27. Epub 2007 Jun 7. [PubMed]
[9] Division of Human Development, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention. Attention-Deficit/Hyperactivity Disorder (ADHD); Data and Statistics. [cdc]
[10] de Diego Otero Y. An abnormal nitric oxide metabolism contributes to brain oxidative stress in the mouse model for the Fragile X Syndrome, a possible role in intellectual disability. Oxidative Medicine and Cellular Longevity. 2015 Sept 15. [pdf]
[11] Joseph N, Zhang-James Y, Perl A, Faraone SV. Oxidative Stress and ADHD: A Meta-Analysis. Nutrients. 2012 Apr; 4(4): 243–257. [pubmed]
[12] Selek S, Savas HA, Gergerlioglu HS, Bulut M, Yilmaz HR. Oxidative imbalance in adult attention deficit/hyperactivity disorder. Biological Psychology. 2008 Oct;79(2):256–259. [link]
[13] Donev R, Thome J. Inflammation: good or bad for ADHD? Gastroenterology. 2007 July; 133 (1): 195–206. [link]
[14] Marazziti D, Baroni S, Picchetti M, Landi P, Silvestri S, Vatteroni E, Catena Dell'Osso M. Psychiatric disorders and mitochondrial dysfunctions. Nutrients. 2012 Apr; 4(4): 243–257. [PubMed]
[15] Kelly AS, Rudser KD, Dengel DR, Kaufman CL, Reiff MI, Norris AL, Metzig AM, Steinberger J. Cardiac autonomic dysfunction and arterial stiffness among children and adolescents with attention deficit hyperactivity disorder treated with stimulants. Journal of Pediatrics. 2014 Oct;165(4):755-9. Epub 2014 Jul 9. [PubMed]
[16] Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, Sheth KK, Simmons AL, Wingertzahn MA, Boyle JM. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol. 2009 Sep;124(3 Suppl):S43-70. doi: 10.1016/j.jaci.2009.05.013. Epub 2009 Jul 9.
[17] Soni, A. Allergic Rhinitis: Trends in Use and Expenditures, 2000 and 2005. Medical Expenditure Panel Survey. Agency for Healthcare Research and Quality STATISTICAL BRIEF #204. [MEPS]
[18] Schaffer FM. National Impact of Allergies. Accessed 2016 Jan 26. [pdf]
[19] Salvemini D, Ischiropoulos H, Cuzzocrea S. Roles of nitric oxide and superoxide in inflammation. Methods Mol Biol. 2003;225:291-303. [PubMed]

[20] Kang BH, Chen SS, Jou LS, Weng PK, Wang HW. Immunolocalization of inducible nitric oxide synthase and 3-nitrotyrosine in the nasal mucosa of patients with rhinitis. Eur Arch Otorhinolaryngol. 2000;257(5):242-6. [PubMed]
[21] Sato M, Fukuyama N, Sakai M, Nakazawa H. Increased nitric oxide in nasal lavage fluid and nitrotyrosine formation in nasal mucosa--indices for severe perennial nasal allergy. Clin Exp Allergy. 1998 May;28(5):597-605. [PubMed]
[22] Tanou K, Koutsokera A, Kiropoulos TS, Maniati M, Papaioannou AI, Georga K, Zarogiannis S, Gourgoulianis KI, Kostikas K. Inflammatory and oxidative stress biomarkers in allergic rhinitis: the effect of smoking. Clin Exp Allergy. 2009 Mar;39(3):345-53. [PubMed]
[23] Aguilera-Aguirre L, Bacsi A, Saavedra-Molina A, Kurosky A, Sur S, Boldogh I. Mitochondrial dysfunction increases allergic airway inflammation. J Immunol. 2009 Oct 15; 183(8): 5379–5387. [PubMed]
[24] Emin O, Esra G, Ufuk E, Demiri A, Ayhan S, Rusen DM. Int J Pediatr Otorhinolaryngol. Autonomic dysfunction and clinical severity of disease in children with allergic rhinitis. 2012 Aug;76(8):1196-200. [PubMed]
[25] Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. NCHS Data Brief. No. 121, May 2013. [CDC]
[26] Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013 Nov;167(11):1026-31. [PubMed]
[27] Kato T, Tada-Oikawa S, Wang L, Murata M, Kuribayashi K. Endocrine disruptors found in food contaminants enhance allergic sensitization through an oxidative stress that promotes the development of allergic airway inflammation. Toxicol Appl Pharmacol. 2013 Nov 15;273(1):10-8. doi: 10.1016/j.taap.2013.08.029. Epub 2013 Sep 10. [PubMed]
[28] MacDonald TT, Monteleone G. Immunity, Inflammation, and Allergy in the Gut. Science 25 March 2005: Vol. 307 no. 5717 pp. 1920-1925. [link]
[29] Jenkins HR, Pinco JR, Soothill JF, Milla PJ, Harries JT. Food allergy: the major cause of infantile colitis. Archives of Disease in Childhood, 1984, 59, 326-329. [pdf]
[30] Miles MV, Putnam PE, Miles L, Tang PH, DeGrauw AJ, Wong BL, Horn PS, Foote HL, Rothenberg ME. Acquired coenzyme Q10 deficiency in children with recurrent food intolerance and allergies. Mitochondrion. Jan 2011;11(1): 127–135. [Link]
[31] De Luca L, Foggia L, Chiummariello S. [A correlation between food allergy, the autonomic nervous system and the central nervous system: a study of 8 patients in childhood][Article in Italian]. Pediatr Med Chir. 1996 Nov-Dec;18(6):565-71. [PubMed]
[32] National Institute of Neurological Disorders and Stroke. Disorders A-Z; NINDS Alzheimer's Disease Information Page. Page modified 2016 Feb 2. Accessed 2016 Mar 23.
[33] Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. Cold Spring Harb Perspect Med. 2012 Jan;2(1):a006346. doi: 10.1101/cshperspect.a006346. [PubMed]
[34] Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013 May 7;80(19):1778-83. [PubMed]
[35] Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29(1-2):125-32. Epub 2007 Oct 29. [PubMed]
[36] Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States.N Engl J Med. 2013 Apr 4;368(14):1326-34. doi: 10.1056/NEJMsa1204629. [PubMed]
[37] Good PF, Werner P, Hsu A, Olanow CW, Perl DP. Evidence of neuronal oxidative damage in Alzheimer's disease. Am J Pathol. 1996 Jul; 149(1): 21–28. [PubMed]
[38] Reyes JF, Fu Y, Vana L, Kanaan NM, Binder LI. Tyrosine nitration within the proline-rich region of Tau in Alzheimer's disease. Am J Pathol. 2011 May;178(5):2275-85. doi: 10.1016/j.ajpath.2011.01.030. [PubMed]

[39] Smith MA, Richey Harris PL, Sayre LM, Beckman JS, Perry G. Widespread peroxynitrite-mediated damage in Alzheimer's disease. J Neurosci. 1997 Apr 15;17(8):2653-7. [PubMed]
[40] Reynolds MR, Berry RW, Binder LI. Site-specific nitration and oxidative dityrosine bridging of the tau protein by peroxynitrite: implications for Alzheimer's disease. Biochemistry. 2005 Feb 8;44(5):1690-700. [PubMed]
[41] Tohgi H, Abe T, Yamazaki K, Murata T, Ishizaki E, Isobe C. Alterations of 3-nitrotyrosine concentration in the cerebrospinal fluid during aging and in patients with Alzheimer's disease. Neurosci Lett. 1999 Jul 2;269(1):52-4. [PubMed]
[42] Hensley K, Maidt ML, Yu Z, Sang H, Markesbery WR, Floyd RA. Electrochemical Analysis of Protein Nitrotyrosine and Dityrosine inthe Alzheimer Brain Indicates Region-Specific Accumulation. J Neurosci. 1998 Oct 15; 18(20):8126–8132. [pdf]
[43] Butterfield DA, Reed T, Sultana R. Roles of 3-nitrotyrosine- and 4-hydroxynonenal-modified brain proteins in the progression and pathogenesis of Alzheimer's disease. Free Radical Research. 2011 Jan; 45(1):59–72. [pdf]
[44] Su JH, Deng G, Cotman CW. Neuronal DNA damage precedes tangle formation and is associated with up-regulation of nitrotyrosine in Alzheimer's disease brain. Brain Research. 1997 Nov;774 (1–2, 7):193–199. [link]
[45] Lüth HJ, Münch G, Arendt T. Aberrant expression of NOS isoforms in Alzheimer's disease is structurally related to nitrotyrosine formation. Brain Research. 2002 Oct; 953(1–2, 25):135–143. [link]
[46] Birnboim HC, Lemay AM, Lam DK, Goldstein R, Webb JR. Cutting edge: MHC class II-restricted peptides containing the inflammation-associated marker 3-nitrotyrosine evade central tolerance and elicit a robust cell-mediated immune response. J Immunol. 2003 Jul 15;171(2):528-32. [PubMed] [FullText]
[47] Heales SJ, Bolanos JP, Stewart VC, Brookes PS, Land JM, Clark JB. Nitric oxide, mitochondria and neurological disease. Biochim Biophys Acta. 1999; 1410: 215–228. [PubMed] [FullText]
[48] Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med. 1997;23(1):134-47. [PubMed]
[49] Miklossy J. Chronic inflammation and amyloidogenesis in Alzheimer's disease -- role of Spirochetes. J Alzheimers Dis. 2008 May;13(4):381-91. [PubMed]
[50] Hensley K, Maidt ML, Yu Z, Sang H, Markesbery WR, Floyd RA. Electrochemical Analysis of Protein Nitrotyrosine and Dityrosine inthe Alzheimer Brain Indicates Region-Specific Accumulation. J Neurosci. 1998 Oct 15; 18(20):8126–8132. [pdf]
[51] Maruszak A, Żekanowski C. Mitochondrial dysfunction and Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Mar 30;35(2):320-30. [PubMed]
[52] Moreira PI, Carvalho C, Zhu X, Smith MA, Perry G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochim Biophys Acta. 2010 Jan;1802(1):2-10. [PubMed]
[53] Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta. 2014 Aug;1842(8):1240-7. [PubMed]
[54] Algotsson A, Viitanen M, Winblad B, Solders G.Autonomic dysfunction in Alzheimer's disease. Acta Neurol Scand. 1995 Jan;91(1):14-8. [PubMed]
[55] Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, Severity, and Comorbidity of Twelve-month DSM-IV Disorders in the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry. 2005 Jun;62(6):617-27. [PubMed]
[56] Burden of Mental Illness. Centers for Disease Control and Prevention. October 4, 2013. [CDC]
[57] Gauthier C, Hassler C, Mattar L, Launay JM, Callebert J, Steiger H, Melchior JC, Falissard B, Berthoz S, Mourier-Soleillant V, Lang F, Delorme M, Pommereau X, Gerardin P, Bioulac S, Bouvard M; EVHAN Group, Godart N. Symptoms of depression and anxiety in anorexia nervosa: links with plasma tryptophan and serotonin metabolism. Psychoneuroendocrinology. 2014 Jan;39:170-8. doi: 10.1016/j.psyneuen.2013.09.009. Epub 2013 Sep 17. [PubMed]
[58] Oosthuizen F, Wegener G, Harvey BH. Nitric oxide as inflammatory mediator in post-traumatic stress disorder (PTSD): evidence from an animal model. Neuropsychiatr Dis Treat. 2005 Jun; 1(2): 109–123.

[59] Salim S, Sarraj N, Taneja M, Saha K, Tejada-Simon MV, Chugh G. Moderate treadmill exercise prevents oxidative stress-induced anxiety-like behavior in rats. Behav Brain Res. 2010 Apr 2;208(2):545-52. doi: 10.1016/j.bbr.2009.12.039. Epub 2010 Jan 12. [PubMed] [pdf]
[60] Bouayed J, Rammal H, Soulimani R. Oxidative stress and anxiety: relationship and cellular pathways. Oxid Med Cell Longev. 2009 Apr-Jun;2(2):63-7. [PubMed]
[61] Salim S, Taneja M, Chugh G, Saha K, Sarraj N, Vollert C, Tejada-Simon MV, Eikenburg DC, Hovatta I. A Potential Protective Role of RGS2 in Oxidative-Stress Mediated Anxious Behavior in Rats. FASEB J; April 2009:23. [Link]
[62] Camacho A. Is anxious-depression an inflammatory state? Med Hypotheses. 2013 Oct;81(4):577-81. [PubMed]
[63] Anglin RE, Garside SL, Tarnopolsky MA, Mazurek MF, Rosebush PI. The psychiatric manifestations of mitochondrial disorders: a case and review of the literature.J Clin Psychiatry. 2012 Apr;73(4):506-12. [PubMed]
[64] Bajkó Z, Szekeres CC, Kovács KR, Csapó K, Molnár S, Soltész P, Nyitrai E, Magyar MT, Oláh L, Bereczki D, Csiba L. Anxiety, depression and autonomic nervous system dysfunction in hypertension. J Neurol Sci. 2012 Jun 15;317(1-2):112-6. doi: 10.1016/j.jns.2012.02.014. Epub 2012 Mar 16. [PubMed]
[65] Anxiety and Depression Association of America. Facts and Statistics. 2014 Sept. Webpage. [link]
[66] Bourdon KH, Rae DS, Locke BZ, Narrow WE, Regier DA. Estimating the Prevalence of Mental Disorders in U.S. Adults from the Epidemiologic Catchment Area Survey. Public Health Rep. 1992 Nov-Dec; 107(6): 663–668. [PubMed]
[67] Liu F, Havens J, Yu Q, Wang G, Davisson RL, Pickel VM, Iadecola C. The link between angiotensin II-mediated anxiety and mood disorders with NADPH oxidase-induced oxidative stress. Int J Physiol Pathophysiol Pharmacol. 2012;4(1):28-35. Epub 2012 Feb 15. [PubMed]
[68] Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008 Jan;58(1):26-35. doi: 10.1002/art.23176. [PubMed]
[69] Cooper C, Javaid MK, Arden N. Atlas of Osteoarthritis; Chapter 2: Epidemiology of osteoarthritis. Springer Healthcare; 2014. [PDF]
[70] Centers for Disease Control and Prevention. Osteoarthritis: Costs. [CDC]
[71] Szabó C, Scott GS, Virág L, Egnaczyk G, Salzman AL, Shanley TP, Haskó G. Suppression of macrophage inflammatory protein (MIP)-1alpha production and collagen-induced arthritis by adenosine receptor agonists. Br J Pharmacol. 1998 Sep;125(2):379-87. [PubMed]
[72] Whiteman M, Spencer JP, Zhu YZ, Armstrong JS, Schantz JT. Peroxynitrite-modified collagen-II induces p38/ERK and NF-kappaB-dependent synthesis of prostaglandin E2 and nitric oxide in chondrogenically differentiated mesenchymal progenitor cells. Osteoarthritis Cartilage. 2006 May;14(5):460-70. Epub 2006 Jan 19. [PubMed] [FullText]
[73] Abramson SB. Nitric oxide in inflammation and pain associated with osteoarthritis. Arthritis Res Ther. 2008; 10(Suppl 2): S2. Published online 2008 Oct 17. doi: 10.1186/ar2463. [PubMed]
[74] Greenacre SAB, Ischiropoulos H. Tyrosine nitration: Localisation, quantification, consequences for protein function and signal transduction. Free Radic Res. 2001 Jun;34(6):541-81. [PubMed] [FullText]
[75] Khan F, Siddiqui AA. Prevalence of anti-3-nitrotyrosine antibodies in the joint synovial fluid of patients with rheumatoid arthritis, osteoarthritis and systemic lupus erythematosus. Clin Chim Acta. 2006 Aug;370(1-2):100-7. Epub 2006 Mar 2. [PubMed]
[76] Ziskoven C, Jäger M, Zilkens C, Bloch W, Brixius K, Krauspe R. Oxidative stress in secondary osteoarthritis: from cartilage destruction to clinical presentation? Orthop Rev (Pavia). 2010 Sep 23; 2(2): e23. [PubMed]
[77] Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis. 2013 Apr; 5(2): 77–94. [PubMed]
[78] Szabó C, Scott GS, Virág L, Egnaczyk G, Salzman AL, Shanley TP, Haskó G. Suppression of macrophage inflammatory protein (MIP)-1alpha production and collagen-induced arthritis by adenosine receptor agonists. Br J Pharmacol. 1998 Sep;125(2):379-87. [PubMed]
[79] Blanco FJ, López-Armada MJ, Maneiro E. Mitochondrial dysfunction in osteoarthritis. Mitochondrion. 2004 Sep;4(5-6):715-28. Epub 2004 Oct 1. [PubMed]

[80] Yun AJ, Lee PY, Doux J. Osteoarthritis: an example of phenoptosis through autonomic dysfunction? Med Hypotheses. 2006;67(5):1079-85. Epub 2006 Apr 3. [PubMed]
[81] Moorman JE, Akinbami LJ, Bailey CM, et al. National Surveillance of Asthma: United States, 2001–2010. National Center for Health Statistics. Vital Health Stat 3(35). 2012. [CDC]
[82] Centers for Disease Control and Prevention; Asthma Rates Continue to Rise. Vital Signs; Morbidity and Mortality Weekly Report (MMWR). 2011 May 3.U.S. [CDC]
[83] Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol. 2011 Jan;127(1):145-52. doi: 10.1016/j.jaci.2010.10.020. [PubMed]
[84] Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. J Allergy Clin Immunol. 2002 Sep;110(3):349-56. \[PubMed] [FullText]
[85] Baraldi E, Giordano G, Pasquale MF, Carraro S, Mardegan A, Bonetto G, Bastardo C, Zacchello F, Zanconato S. 3-Nitrotyrosine, a marker of nitrosative stress, is increased in breath condensate of allergic asthmatic children. Allergy. 2006 Jan;61(1):90-6. [PubMed] [pdf]
[86] Saleh D, Ernst P, Lim S, Barnes PJ, Giaid A. Increased formation of the potent oxidant peroxynitrite in the airways of asthmatic patients is associated with induction of nitric oxide synthase: effect of inhaled glucocorticoid. FASEB J. 1998 Aug;12(11):929-37. [PubMed] [FullText]
[87] Kanazawa H, Shiraishi S, Hirata K, Yoshikawa J. Decreased peroxynitrite inhibitory activity in induced sputum in patients with bronchial asthma.Thorax. 2002 Jun;57(6):509-12. [PubMed]
[88] Hanazawa T, Kharitonov SA, Barnes PJ. Increased nitrotyrosine in exhaled breath condensate of patients with asthma. Am J Respir Crit Care Med. 2000 Oct;162(4 Pt 1):1273-6. [PubMed]
[89] Kaminsky DA, Mitchell J, Carroll N, James A, Soultanakis R, Janssen Y. Nitrotyrosine formation in the airways and lung parenchyma of patients with asthma. J Allergy Clin Immunol. 1999 Oct;104(4 Pt 1):747-54. [PubMed]
[90] Sahiner UM, Birben E, Erzurum S, Sackesen C, Kalayci O. Oxidative Stress in Asthma. World Allergy Organ J. 2011 Oct; 4(10): 151–158. [link]
[91] Murdoch JR, Lloyd CM. Chronic inflammation and asthma. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis; Volume 690, Issues 1–2, 7 August 2010, Pages 24–39; Chronic inflammation, mutation and human disease. [link]
[92] Reddy PH. Mitochondrial Dysfunction and Oxidative Stress in Asthma: Implications for Mitochondria- Targeted Antioxidant Therapeutics. Pharmaceuticals (Basel). 2011 Mar; 4(3): 429–456. [link]
[93] Jartti T. Clin Physiol. Asthma, asthma medication and autonomic nervous system dysfunction. 2001 Mar;21(2):260-9. [PubMed]
[94] National Institute of Neurological Disorders and Stroke. Disorders A-Z; NINDS Autism Spectrum Disorder Information Page. Page modified 2016 Feb 1. Accessed 2016 Mar 23.
[95] Baio J. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. Centers for Disease Condrol and Prevention; Morbidity and Mortality Weekly Report (MMWR); Surveillance Summaries. March 28, 2014 / 63(SS02);1-21. [CDC]
[96] Rice C. Prevalence of Autism Spectrum Disorders --- Autism and Developmental Disabilities Monitoring Network, Six Sites, United States, 2000. CDC: MMWR; Surveillance Summaries; Feb 9, 2007 / 56(SS01);1-11. [CDC]
[97] Leigh JP, Du J. Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States. J Autism Dev Disord. 2015 Dec;45(12):4135-9. doi: 10.1007/s10803-015-2521-7. [PubMed]
[98] Essa MM, Subash S, Braidy N, Al-Adawi S, Lim CK, Manivasagam T, Guillemin GJ. Role of NAD+, Oxidative Stress, and Tryptophan Metabolism in Autism Spectrum Disorders. Int J Tryptophan Res. 2013; 6(Suppl 1): 15–28. Published online 2013 Jul 21. doi: 10.4137/IJTR.S11355 [PubMed]
[99] Sajdel-Sulkowska EM, Boguslaw L, Windom H, Tapan A, Woody M. Oxidative Stress in Autism: Elevated Cerebellar 3-nitrotyrosine Levels. Am J of Biochemistry and Biotechnology. 2008 Feb; 4(2). [link] [pdf]

[100] Rose S, Melnyk S, Pavliv O, Bai S, Nick TG, Frye RE, James SJ. Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. Transl Psychiatry. 2012 Jul; 2(7): e134. Published online 2012 Jul 10. doi: 10.1038/tp.2012.61 [PubMed]
[101] Shaw W. Evidence that Increased Acetaminophen use in Genetically Vulnerable Children Appears to be a Major Cause of the Epidemics of Autism, Attention Deficit with Hyperactivity, and Asthma. J of Restorative Med. 2013; 2:1-16. [link]
[102] Blaylock RL. A possible central mechanism in autism spectrum disorders, part 2: immunoexcitotoxicity. Alternative Therapies in Health and Medicine; 2009 Jan/Feb; 15(1): 60-67. [pdf]
[103] Rossignol DA, Frye RE. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. [link]
[104] Cheshire WP. Highlights in clinical autonomic neuroscience: new insights into autonomic dysfunction in autism. Auton Neurosci. 2012 Nov 2;171(1-2):4-7. [PubMed]
[105] Schmidt CW. Questions Persist: Environmental Factors in Autoimmune Disease. Environ Health Perspect 119:a248-a253 (2011). [link]
[106] American Autoimmune Related Diseases Association (AARDA). Autoimmune Statistics. 2015. [link]
[107] Oleszak EL, Zaczynska E, Bhattacharjee M, Butunoi C, Legido A, Katsetos CD. Inducible nitric oxide synthase and nitrotyrosine are found in monocytes/macrophages and/or astrocytes in acute, but not in chronic, multiple sclerosis. Clin Diagn Lab Immunol. 1998 Jul;5(4):438-45. [PubMed]
[108] Oates JC, Christensen EF, Reilly CM, Self SE, Gilkeson GS. Prospective measure of serum 3-nitrotyrosine levels in systemic lupus erythematosus: correlation with disease activity. Proc Assoc Am Physicians. 1999 Nov-Dec;111(6):611-21. [PubMed]
[109] Ahmad R, Rasheed Z, Ahsan H. Biochemical and cellular toxicology of peroxynitrite: implications in cell death and autoimmune phenomenon. Immunopharmacol Immunotoxicol. 2009;31(3):388-96. doi: 10.1080/08923970802709197. [PubMed]
[110] Keng T, Privalle CT, Gilkeson GS, Weinberg JB. Peroxynitrite formation and decreased catalase activity in autoimmune MRL-lpr/lpr mice. Mol Med. 2000 Sep;6(9):779-92. [PubMed]
[111] van der Veen RC, Hinton DR, Incardonna F, Hofman FM. Extensive peroxynitrite activity during progressive stages of central nervous system inflammation. J Neuroimmunol. 1997 Jul;77(1):1-7. [PubMed]
[112] Miller MJ, Thompson JH, Zhang XJ, Sadowska-Krowicka H, Kakkis JL, Munshi UK, Sandoval M, Rossi JL, Eloby-Childress S, Beckman JS, et al. Role of inducible nitric oxide synthase expression and peroxynitrite formation in guinea pig ileitis. Gastroenterology. 1995 Nov;109(5):1475-83. [PubMed]
[113] Bachmaier K, Neu N, Pummerer C, Duncan GS, Mak TW, Matsuyama T, Penninger JM. iNOS expression and nitrotyrosine formation in the myocardium in response to inflammation is controlled by the interferon regulatory transcription factor 1. Circulation. 1997 Jul 15;96(2):585-91. [PubMed]
[114] Kumagai S, Jikimoto T, Saegusa J. [Pathological roles of oxidative stress in autoimmune diseases]. Rinsho Byori. 2003 Feb;51(2):126-32. [PubMed]
[115] Ishihara K, Hirano T. IL-6 in autoimmune disease and chronic inflammatory proliferative disease. Cytokine & Growth Factor Reviews; Volume 13, Issues 4–5, August–October 2002, Pages 357–368; Cytokines in Autoimmune Disease. [PubMed]
[116] Maoa P, Reddy PH. Is multiple sclerosis a mitochondrial disease? Biochim Biophys Acta. 2010 Jan; 1802(1): 66–79. [PubMed]
[117] Stojanovich L, Milovanovich B, de Luka SR, Popovich-Kuzmanovich D, Bisenich V, Djukanovich B, Randjelovich T, Krotin M. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. Lupus March 2007 vol. 16 no. 3 181-185. [link]
[118] Neuroscience News. Neurological Disorders. Accessed 2016 Mar 24. [Link]
[119] PubMed Health. Bipolar Disorder; About Bipolar Disorder. Accessed 2016 Mar 23. [PubMed]
[120] Marvel CL, Paradiso S. Cognitive and neurological impairment in mood disorders. Psychiatr Clin North Am. 2004 Mar;27(1):19-36, vii-viii. [PubMed]
[121] Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry. 2007 Sep;64(9):1032-9. [PubMed]
[122] Dilsaver SC. An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. J Affect Disord. 2011 Mar;129(1-3):79-83. doi: 10.1016/j.jad.2010.08.030. [PubMed]

[123] Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Gonçalves CA, Young LT, Yatham LN. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J Psychiatry Neurosci. 2009 Jul;34(4):263-71. [PubMed]
[124] Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res. 2014 Aug 15;218(1-2):61-8. doi: 10.1016/j.psychres.2014.04.005. Epub 2014 Apr 13. [PubMed]
[125] Tang V, Wang JF (2012) Oxidative Stress in Bipolar Disorder. Biochem Anal Biochem S2-002. Doi:10.4172/2161-1009.S2-002. [pdf]
[126] Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yücel M, Gama CS, Dodd S, Dean B, P.V.S. Magalhães PVS, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011 Jan;35(3):804-17. [PubMed]
[127] Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, Kupfer DJ. Can Bipolar Disorder Be viewed as a multi-system inflammatory disease? Arch Immunol Ther Exp (Warsz). 2004 Nov-Dec;52(6):379-88. [PubMed]
[128] Clay HB, Sillivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. Arthritis Rheum. 2011 Aug;63(8):2172-82. [PubMed]
[129] Yun AJ, Lee PY, Doux J. Osteoarthritis: an example of phenoptosis through autonomic dysfunction? Med Hypotheses. 2006;67(5):1079-85. Epub 2006 Apr 3. [PubMed]
[130] Erie JC, Baratz KH, Hodge DO, Schleck CD, Burke JP. Incidence of cataract surgery from 1980 through 2004: 25-year population-based study. J Cataract Refract Surg. 2007 Jul;33(7):1273-7. [PubMed]
[131] Wittenborn J, Rein D. Cost of Vision Problems: The Economic Burden of Vision Loss and Eye Disorders in the United States. [pdf]
[132] Ho MC, Peng YJ, Chen SJ, Chiou SH. Senile cataracts and oxidative stress. J of Clinical Gerontology and Geriatrics. 2010 Sept;1(1):17–21. [link]
[133] Hao LN, Ling YL, He SZ, Mao QY, Liang JQ. [Peroxynitrite-induced formation of diabetic cataract and its prevention by puerarin in rat]. [Article in Chinese]. Zhonghua Yan Ke Za Zhi. 2004 May;40(5):311-6. [PubMed]
[134] Berthoud VM, Beyer, EC. Oxidative Stress, Lens Gap Junctions, and Cataracts. Antioxid Redox Signal. 2009 Feb; 11(2): 339–353. doi: 10.1089/ars.2008.2119 [PubMed]
[135] Kim BG, Yoo YS, Kim HK. The Role of Nitric Oxide in the Cataract Development: A Possible Mechanism of Lens Opacity. [Korean.] J Korean Ophthalmol Soc. 2002 Apr; 43(4):757-763. [link]
[136] Drel VR, Pacher P, Ali TK, Shin J, Julius U, El-Remessy AB, Obrosova IG. Aldose reductase inhibitor fidarestat counteracts diabetes-associated cataract formation, retinal oxidative-nitrosative stress, glial activation, and apoptosis. Int J Mol Med. 2008 Jun;21(6):667-76. [PubMed]
[137] Varma SD, Hegde KR. Lens thiol depletion by peroxynitrite. Protective effect of pyruvate. Mol Cell Biochem. 2007 Apr;298(1-2):199-204. Epub 2006 Nov 17. [PubMed] [link]
[138] Hao LN, Ling YQ, Mao QY, Ling YL, He SZ. The antagonism of cholecystokinin octapeptide-8 to the peroxynitrite oxidation on a diabetic cataractal rat model. Chin Med J (Engl). 2006 Sep 5;119(17):1451-7. [PubMed]
[139] Paik DC, Choi C, Merriam JC, Dillon JP. Detection of 3-Nitro-Tyrosine in the Cataractous Lens. Investigative Ophthalmology & Visual Science. 2003 May;44:2349. [link]
[140] Harding JJ. Conformational Changes in Human Lens Proteins in Cataract. Biochem. J. 1972; 129: 97-100. [PubMed] [pdf]
[141] Spector A. Oxidative stress-induced cataract: mechanism of action. FASEB J. 1995 Sep;9(12):1173-82. [PubMed]
[142] Agrawal R, Murthy S, Ganesh SK, Phaik CS, Sangwan V, Biswas J. Cataract Surgery in Uveitis. International Journal of Inflammation; Volume 2012 (2012), Article ID 548453, 16 pages. [link]

[143] Saunders C, Smith L, Wibrand F, Ravn K, Bross P, Thiffault I, Christensen M, Atherton A, Farrow E, Miller N, Kingsmore SF, Ostergaard E. CLPB variants associated with autosomal-recessive mitochondrial disorder with cataract, neutropenia, epilepsy, and methylglutaconic aciduria. Am J Hum Genet. 2015 Feb 5;96(2):258-65. doi: 10.1016/j.ajhg.2014.12.020. Epub 2015 Jan 15. [PubMed]
[144] Heckmann JM, Carr JA, Bell N. Hereditary sensory and autonomic neuropathy with cataracts, mental retardation, and skin lesions: Five cases. Neurology July 1995 vol. 45 no. 7 1405-1408. [link]
[145] Green PHR, Stavropoulos SN, Panagi SG, Goldstein SL, Mcmahon DJ, Absan H, Neugut AI. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol. 2001 Jan;96(1):126-31.
[PubMed]
[146] University of Chicago Celiac Disease Center. Celiac Disease Facts and Figures. Accessed 2016 Feb 27. [pdf]
[147] Riddle MS, Murray JA, Porter CK. The incidence and risk of celiac disease in a healthy US adult population. Am J Gastroenterol. 2012 Aug;107(8):1248-55. [PubMed]
[148] Celiac Support Association, Inc. Celiac Disease Facts. [link]
[149] Ferretti G, Bacchetti T, Masciangelo S, Saturni L. Celiac Disease, Inflammation and Oxidative Damage: A Nutrigenetic Approach. Nutrients. 2012 Apr; 4(4): 243–257. Published online 2012 Mar 27. doi: 10.3390/nu4040243. [PubMed]
[150] ter Steege J, Buurman W, Arends JW, Forget P. Presence of inducible nitric oxide synthase, nitrotyrosine, CD68, and CD14 in the small intestine in celiac disease. Lab Invest. 1997 Jul;77(1):29-36. [PubMed]
[151] Murray IA, Daniels I, Coupland K, Smith JA, Long RG. Increased activity and expression of iNOS in human duodenal enterocytes from patients with celiac disease. Am J Physiol Gastrointest Liver Physiol. 2002 Aug;283(2):G319-26. [PubMed] [FullText]
[152] ter Steege JC, Koster-Kamphuis L, van Straaten EA, Forget PP, Buurman WA. Nitrotyrosine in plasma of celiac disease patients as detected by a new sandwich ELISA. Free Radic Biol Med. 1998 Nov 15;25(8):953-63. [PubMed]
[153] Cervio E, Volta U, Verri M, Boschi F, Pastoris O, Granito A, Barbara G, Paris C, Felicani C, Tonini M, De Giorgio R. Sera of Patients With Celiac Disease and Neurologic Disorders Evoke a Mitochondrial-Dependent Apoptosis In Vitro. Gastroenterology;Volume 133, Issue 1, July 2007, Pages 195–206. [link]
[154] Tursi A, Giorgetti GM, Iani C, Arciprete F, Brandimarte G, Capria A, Fontana L. Peripheral Neurological Disturbances, Autonomic Dysfunction, and Antineuronal Antibodies in Adult Celiac Disease Before and After a Gluten-Free Diet. Digestive Diseases and Sciences; October 2006, Volume 51, Issue 10, pp 1869-1874. [link]
[155] Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr. 2007 Jun 8;5:5. [PubMed]
[156] Vincent A, Brimmer DJ, Whipple MO, Jones JF, Boneva R, Lahr BD, Maloney E, St. Sauver JL, Reeves WC. Prevalence, Incidence, and Classification of Chronic Fatigue Syndrome in Olmsted County, Minnesota, as Estimated Using the Rochester Epidemiology Project. Mayo Clin Proc. 2012 Dec; 87(12): 1145–1152. [link]
[157] Lin JM, Resch SC, Brimmer DJ, Johnson A, Kennedy S, Burstein N, Simon CJ. The economic impact of chronic fatigue syndrome in Georgia: direct and indirect costs. Cost Eff Resour Alloc. 2011 Jan 21;9(1):1. doi: 10.1186/1478-7547-9- 1. [PubMed]
[158] Pall ML. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. Medical Hypotheses. 2001 Aug;57(2):139–145. [link]
[159] Pall ML. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. Med Hypotheses. 2000 Jan;54(1):115-25. [PubMed]
[160] Pall ML, Satterlee JD. Elevated nitric oxide/peroxynitrite mechanism for the common etiology of multiple chemical sensitivity, chronic fatigue syndrome, and posttraumatic stress disorder. Ann N Y Acad Sci. 2001 Mar;933:323-9. [PubMed]
[161] Maes M, Mihaylova I, Leunis JC. Chronic fatigue syndrome is accompanied by an IgM-related immune response directed against neopitopes formed by oxidative or nitrosative damage to lipids and proteins. Neuro Endocrinol Lett. 2006 Oct;27(5):615-21. [PubMed] [pdf]

[162] Maes M, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Increased plasma peroxides as a marker of oxidative stress in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Med Sci Monit. 2011 Apr;17(4):SC11-5. [PubMed]
[163] Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. Free Radic Biol Med. 2005 Sep 1;39(5):584-9. [PubMed]
[164] Buchwald D, Wener MH, Pearlman T, Kith P. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. The Journal of Rheumatology [1997, 24(2):372-376]. [link]
[165] Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. Int J Clin Exp Med. 2009; 2(1): 1–16. [link]
[166] Newton JL, Okonkwo O, Sutcliffe K, Seth A, Shin J, Jones DE. Symptoms of autonomic dysfunction in chronic fatigue syndrome. QJM. 2007 Aug;100(8):519-26. Epub 2007 Jul 7. [PubMed]
[167] Marelli A, Gilboa S, Devine O, et al. Estimating The Congenital Heart Disease Population In The United States In 2010 - What Are The Numbers?. J Am Coll Cardiol. 2012;59(13s1):E787. doi:10.1016/S0735-1097(12)60788-8.
[168] Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime Prevalence of Congenital Heart Disease in the General Population From 2000 to 2010. Circulation. 2014; 130: 749-756. [link]
[169] Garson A Jr, Allen HD, Gersony WM, Gillette PC, Hohn AR, Pinsky WW, Mikhail O. The cost of congenital heart disease in children and adults. A model for multicenter assessment of price and practice variation. Arch Pediatr Adolesc Med. 1994 Oct;148(10):1039-45. [PubMed]
[170] Fratz S, Fineman JR, Görlach A, Sharma S, Oishi P, Schreiber C, Kietzmann T, Adatia I, Hess J, Black SM. Early Determinants of Pulmonary Vascular Remodeling in Animal Models of Complex Congenital Heart Disease. Circulation. 2011 Mar 1; 123(8): 10.1161/CIRCULATIONAHA.110.978528. [PubMed]
[171] Ercan S, Cakmak A, Kösecik M, Erel O. The oxidative state of children with cyanotic and acyanotic congenital heart disease. Anadolu Kardiyol Derg. 2009 Dec;9(6):486-90. [PubMed]
[172] Sharma R, Bolger AP, Li W, Davlouros PA, Volk HD, Poole-Wilson PA, Coats AJS, Gatzoulis MA, Anker SD. Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. The American Journal of Cardiology; Volume 92, Issue 2, 15 July 2003, Pages 188–193. [link]
[173] Black SM, Fineman JR (2014) Mitochondrial Dysfunction and Congenital Heart Disease. Pediat Therapeut 4:199. [link]
[174] Ohuchi H, Takasugi H, Ohashi H, Okada Y, Yamada O, Ono Y, Yagihara T, Echigo S. Stratification of Pediatric Heart Failure on the Basis of Neurohormonal and Cardiac Autonomic Nervous Activities in Patients With Congenital Heart Disease.Circulation.2003; 108: 2368-2376. [link]
[175] Rovina N, Koutsoukou A, Koulouris NG. Inflammation and Immune Response in COPD: Where Do We Stand? Mediators of Inflammation. 2013. Article ID 413735; 9 pages. [Link]
[176] Simpson CR, Hippisley-Cox J, Sheikh A. Trends in the epidemiology of chronic obstructive pulmonary disease in England: a national study of 51 804 patients. Br J Gen Pract. 2010 Jul 1; 60(576): e277–e284. [link]
[177] Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. Clinicoecon Outcomes Res. 2013; 5: 235–245. [link]
[178] Jin H, Webb-Robertson BJ, Peterson ES, Tan R, Bigelow DJ, Scholand MB, Hoidal JR, Pounds JG, Zangar RC. Smoking, COPD, and 3-nitrotyrosine levels of plasma proteins. Environ Health Perspect. 2011 Sep;119(9):1314-20. Doi: 10.1289/ehp.1103745. Epub 2011 Jun 6. [PubMed]
[179] Rytilä P, Rehn T, Ilumets H, Rouhos A, Sovijärvi A, Myllärniemi M, Kinnula VL. Increased oxidative stress in asymptomatic current chronic smokers and GOLD stage 0 COPD. Respir Res. 2006 Apr 28;7:69. [PubMed]
[180] Montes de Oca M, Torres SH, De Sanctis J, Mata A, Hernández N, Tálamo C. Skeletal muscle inflammation and nitric oxide in patients with COPD. Eur Respir J. 2005 Sep;26(3):390-7. [PubMed] [FullText]
[181] Maestrelli P, Páska C, Saetta M, Turato G, Nowicki Y, Monti S, Formichi B, Miniati M, Fabbri LM. Decreased haem oxygenase-1 and increased inducible nitric oxide synthase in the lung of severe COPD patients. Eur Respir J. 2003 Jun;21(6):971-6. [PubMed] [FullText]

[182] MacNee W. Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2(1):50-60. [] [FullText]PubMed
[183] Ichinose M, Sugiura H, Yamagata S, Koarai A, Tomaki M, Ogawa H, Komaki Y, Barnes PJ, Shirato K, Hattori T. Xanthine oxidase inhibition reduces reactive nitrogen species production in COPD airways. Eur Respir J. 2003 Sep;22(3):457- 61. [PubMed] [FullText]
[184] Osoata GO, Hanazawa T, Brindicci C, Ito M, Barnes PJ, Kharitonov S, Ito K. Peroxynitrite elevation in exhaled breath condensate of COPD and its inhibition by fudosteine. Chest. 2009 Jun;135(6):1513-20. doi: 10.1378/chest.08-2105. Epub 2009 Feb 2. [PubMed]
[185] ben Anes A, Fetoui H, Bchir S, ben Nasr H, Chahdoura H, Chabchoub E, Yacoub S, Garrouch A, Benzarti M, Tabka Z, Chahed K. Increased oxidative stress and altered levels of nitric oxide and peroxynitrite in Tunisian patients with chronic obstructive pulmonary disease: correlation with disease severity and airflow obstruction. Biol Trace Elem Res. 2014 Oct;161(1):20-31. doi: 10.1007/s12011-014-0087-4. Epub 2014 Jul 31. [PubMed]
[186] Kanazawa H, S Shiraishi S, Hirata K, Yoshikawa J. Imbalance between levels of nitrogen oxides and peroxynitrite inhibitory activity in chronic obstructive pulmonary disease. Thorax. 2003 Feb; 58(2): 106–109. doi: 10.1136/thorax.58.2.106 [PubMed] [pdf]
[187] Kharitonov SA, Barnes PJ.Nitric oxide, nitrotyrosine, and nitric oxide modulators in asthma and chronic obstructive pulmonary disease. Curr Allergy Asthma Rep. 2003 Mar;3(2):121-9. [PubMed]
[188] Rahman I. The role of oxidative stress in the pathogenesis of COPD: implications for therapy. Treat Respir Med. 2005;4(3):175-200. [PubMed]
[189] Tetley TD. Inflammatory cells and chronic obstructive pulmonary disease. Curr Drug Targets Inflamm Allergy. 2005 Dec;4(6):607-18. [PubMed]
[190] Meyer A, Zoll J, Charles AL, Charloux A, de Blay F, Diemunsch P, Sibilia J, Piquard F, Geny B.
Skeletal muscle mitochondrial dysfunction during chronic obstructive pulmonary disease: central actor and
therapeutic target. Exp Physiol. 2013 Jun;98(6):1063-78. [PubMed]
[191] Van Gestel AJR, Steier J. Autonomic dysfunction in patients with chronic obstructive pulmonary disease (COPD).
J Thorac Dis. 2010 Dec; 2(4): 215–222. [link]
[192] Compton WM, Conway KP, Stinson FS, Grant BF. Changes in the Prevalence of Major Depression and Comorbid Substance Use Disorders in the United States Between 1991–1992 and 2001–2002. The American Journal Of Psychiatry; Dec 2006 Vol 163; Num 12; pp. 2141-2147. [link]
[193] Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry. 2015 Feb;76(2):155-62. doi: 10.4088/JCP.14m09298.
[PubMed] [FullText]
[194] Piletz JE, Halaris A, Iqbal O, Hoppensteadt D, Fareed J, Zhu H, Sinacore J, DeVane CL. Nitric Oxide Branch of Arginine Metabolism in Depression: Effect of Venlafaxine. Intl J Health Science 12/2009; 2:274-281. [link]
[195] Najjar S, Pearlman DM, Hirsch S, Friedman K, Strange J, Reidy J, Khoukaz M, Ferrell RB, Devinsky O, Najjar A, Zagzag D. Brain Biopsy Findings Link Major Depressive Disorder to Neuroinflammation, Oxidative Stress, and Neurovascular Dysfunction: A Case Report. Biol Psychiatry. 2014 Jun 15;75(12):e23-6. doi: 10.1016/j.biopsych.2013.07.041. Epub 2013 Sep 24. [PubMed] [FullText]
[196] Cichoń N, Bijak M, Miller E, Niwald M, Saluk J. Poststroke Depression as a Factor Adversely Affecting the Level of Oxidative Damage to Plasma Proteins during a Brain Stroke. Oxid Med Cell Longev. 2015; Art ID 408745: 10 pps. [link]
[197] Chan SH, Wang LL, Ou CC, Chan JY. Contribution of peroxynitrite to fatal cardiovascular depression induced by overproduction of nitric oxide in rostral ventrolateral medulla of the rat. Neuropharmacology. 2002 Oct;43(5):889-98. [PubMed]
[198] Najjar S, Pearlman DM, Devinsky O, Najjar A, Zagzag D. Neurovascular unit dysfunction with blood-brain barrier hyperpermeability contributes to major depressive disorder: a review of clinical and experimental evidence. J Neuroinflammation. 2013 Dec 1;10:142. doi: 10.1186/1742-2094-10-142. [PubMed]
[199] Tobe EH. Mitochondrial dysfunction, oxidative stress, and major depressive disorder. Neuropsychiatr Dis Treat. 2013;9:567-73. [PubMed]

[200] Vargas HO, Nunes SO, Pizzo de Castro M, Bortolasci CC, Sabbatini Barbosa D, Kaminami Morimoto H, Venugopal K, Dodd S, Maes M, Berk M. Oxidative stress and lowered total antioxidant status are associated with a history of suicide attempts. J Affect Disord. 2013 Sep 25;150(3):923-30. [PubMed]
[201] Michel TM, Pülschen D, Thome J. The role of oxidative stress in depressive disorders. Curr Pharm Des. 2012;18(36):5890-9. [PubMed]
[202] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008 Jan; 9(1): 46–56. [link]
[203] Morris AA, Zhao L, Ahmed Y, Stoyanova N, De Staercke C, Hooper WC, Gibbons G, Din-Dzietham R, Quyyumi A, Vaccarino V.. Association between Depression and Inflammation – Differences by Race and Sex: The META-Health Study. Psychosom Med. 2011 Jul-Aug;73(6):462-8. [PubMed]
[204] Koene S, Kozicz TL, Rodenburg RJT, Verhaak CM, de Vries MC, Wortmann S, van de Heuvel L, Smeitink JAM, Morava E. Major depression in adolescent children consecutively diagnosed with mitochondrial disorder. J Affect Disord. 2009 Apr;114(1-3):327-32. [PubMed]
[205] Koschke M, Boettger MK, Schulz S, Berger, S, Terhaar J, Voss A, Yeragani VK, Bär KJ. Autonomy of Autonomic Dysfunction in Major Depression. Psychosomatic Medicine: October 2009 - Volume 71 - Issue 8 - pp 852-860. [link]
[206] Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014. [link]
[207] CDC's Division of Diabetes Translation. Long-term Trends in Diabetes. October 2014. [pdf]
[208] American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2012. Diabetes Care. 2013 Apr; 36(4): 1033–1046. [link]
[209] Virág L, Szabó E, Gergely P, Szabó C. Peroxynitrite-induced cytotoxicity: mechanism and opportunities for intervention. Toxicol Lett. 2003 Apr 11;140-141:113-24. [PubMed]
[210] Turko IV, Marcondes S, Murad F. Diabetes-associated nitration of tyrosine and inactivation of succinyl-CoA:3-oxoacid CoA-transferase. Am J Physiol Heart Circ Physiol. 2001 Dec;281(6):H2289-94. [PubMed] [FullText]
[211] Wu Y, Tang L, Chen B. Oxidative Stress: Implications for the Development of Diabetic Retinopathy and Antioxidant Therapeutic Perspectives. Oxid Med Cell Longev. 2014; 2014: 752387. Published online 2014 Aug 10. doi: 10.1155/2014/752387 [PubMed]
[212] Jeevendra Martyn JA, Kaneki M, Yasuhara S. Obesity-Induced Insulin Resistance and Hyperglycemia: Etiological Factors and Molecular Mechanisms. Anesthesiology. 2008;109(1):137-148. doi:10.1097/ALN.0b013e3181799d45. [PubMed]
[213] Ceriello A, Mercuri F, Quagliaro L, Assaloni R, Motz E, Tonutti L, Taboga C. Detection of nitrotyrosine in the diabetic plasma: evidence of oxidative stress. Diabetologia. 2001 Jul;44(7):834-8. [PubMed]
[214] Pacher P, Obrosova IG, Mabley JG, Szabó C. Role of Nitrosative Stress and Peroxynitrite in the Pathogenesis of Diabetic Complications. Emerging New Therapeutical Strategies. Curr Med Chem. 2005; 12(3): 267–275. [PubMed]
[215] Szabó C, Mabley JG, Moeller SM, Shimanovich R, Pacher P, Virág L, Soriano FG, Van Duzer JH, Williams W, Salzman AL, Groves JT. Part I: pathogenetic role of peroxynitrite in the development of diabetes and diabetic vascular complications: studies with FP15, a novel potent peroxynitrite decomposition catalyst. Mol Med. 2002 Oct; 8(10): 571–580. [PubMed] [pdf]
[216] Tannous M, Rabini RA, Vignini A, Moretti N, Fumelli P, Zielinski B, Mazzanti L, Mutus B. Evidence for iNOS-dependent peroxynitrite production in diabetic platelets. Diabetologia. 1999 May;42(5):539-44. [PubMed] [pdf]
[217] Marchetti P, Del Guerra S, Marselli L, Lupi R, Masini M, Pollera M, Bugliani M, Boggi U, Vistoli F, Mosca F, Del Prato S. Pancreatic islets from type 2 diabetic patients have functional defects and increased apoptosis that are ameliorated by metformin. J Clin Endocrinol Metab. 2004 Nov;89(11):5535-41. [PubMed] [FullText]
[218] Lyall F, Gibson JL, Greer IA, Brockman DE, Eis AL, Myatt L. Increased nitrotyrosine in the diabetic placenta: evidence for oxidative stress. Diabetes Care. 1998 Oct;21(10):1753-8. [PubMed]
[219] Maritim AC, Sanders RA, Watkins JB 3rd. Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol. 2003;17(1):24-38. [PubMed]

[220] Navarro JF, Mora C. Role of inflammation in diabetic complications. Nephrol. Dial. Transplant. (December 2005) 20 (12): 2601-2604. [link]
[221] Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005 May;115(5):1111-9. [PubMed]
[222] Sivitz WI, Yorek MA. Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. Antioxid Redox Signal. 2010 Apr;12(4):537-77. [PubMed]
[223] Vinik AI, Maser RE, Mitchell BD, Freeman R.Diabetic autonomic neuropathy. Diabetes Care. 2003 May;26(5):1553- 79. [PubMed]
[224] National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Understanding Autoimmune Diseases. 2012 Oct. Accessed 2016 Mar 24. [Link]
[225] DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabet Med. 2006 Aug;23(8):857-66. [PubMed]
[226] Varvarovská J, Racek J, Stetina R, Sýkora J, Pomahacová R, Rusavý Z, Lacigová S, Trefil L, Siala K, Stozický F. Aspects of oxidative stress in children with type 1 diabetes mellitus. Biomed Pharmacother. 2004 Dec;58(10):539-45. [PubMed]
[227] Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulitis and beta-cell loss in type 1 diabetes. Nat Rev Endocrinol. 2009 Apr; 5(4):219-26. doi: 10.1038/nrendo.2009.21. [PubMed]
[228] Weston PJ, Gill GV. Is undetected autonomic dysfunction responsible for sudden death in Type 1 diabetes mellitus? The 'dead in bed' syndrome revisited Diabetic Medicine; Volume 16, Issue 8, pages 626–631, August 1999. [link]
[229] Nehra A, Moreland RB. Neurologic erectile dysfunction. Urol Clin North Am. 2001 May;28(2):289-308. [PubMed] [FullText]
[230]Vlachopoulos C, Rokkas K, Ioakeimidis N, Stefanadis C. Inflammation, metabolic syndrome, erectile dysfunction, and coronary artery disease: common links. Eur Urol. 2007 Dec;52(6):1590-600. Epub 2007 Aug 13. [Link]
[231] Schouten BW, Bohnen AM, Groeneveld FP, Dohle GR, Thomas S, Bosch JL. Erectile dysfunction in the community: trends over time in incidence, prevalence, GP consultation and medication use--the Krimpen study: trends in ED. J Sex Med. 2010 Jul;7(7):2547-53. [PubMed]
[232] Tan HL. Economic cost of male erectile dysfunction using a decision analytic model: for a hypothetical managed-care plan of 100,000 members. Pharmacoeconomics. 2000 Jan;17(1):77-107. [PubMed]
[233] De Young L, Yu D, Bateman RM, Brock GB. Oxidative stress and antioxidant therapy: their impact in diabetes-associated erectile dysfunction. J Androl. 2004 Sep-Oct;25(5):830-6. [PubMed] [FullText]
[234] Agarwal A, Nandipati KC, Sharma RK, Zippe CD, Raina R. Role of oxidative stress in the pathophysiological mechanism of erectile dysfunction. J Androl. 2006 May-Jun;27(3):335-47. Epub 2005 Dec 8. [PubMed] [FullText]
[235] Bivalacqua TJ, Sussan TE, Gebska MA, Strong TD, Berkowitz DE, Biswal S, Burnett AL, Champion HC. Sildenafil inhibits superoxide formation and prevents endothelial dysfunction in a mouse model of secondhand smoke induced erectile dysfunction. J Urol. 2009 Feb;181(2):899-906. doi: 10.1016/j.juro.2008.10.062. Epub 2008 Dec 17. [PubMed]
[236] Jeremy JY, Angelini GD, Khan M, Mikhailidis DP, Morgan RJ, Thompson CS, Bruckdorfer KR, Naseem KM. Platelets, oxidant stress and erectile dysfunction: an hypothesis. Cardiovasc Res. 2000 Apr;46(1):50-4. [PubMed] [FullText]
[237] Khan MA, Thompson CS, Mumtaz FH, Mikhailidis DP, Morgan RJ, Bruckdorfer RK, Naseem KM. The effect of nitric oxide and peroxynitrite on rabbit cavernosal smooth muscle relaxation. World J Urol. 2001 Jun;19(3):220-4. [PubMed]
[238] Azadzoi KM, Schulman RN, Aviram M, Siroky MB. Oxidative stress in arteriogenic erectile dysfunction: prophylactic role of antioxidants. J Urol. 2005 Jul;174(1):386-93. [PubMed]
[239] Vlachopoulos C, Rokkas K, Ioakeimidis N, Stefanadis C. Inflammation, Metabolic Syndrome, Erectile Dysfunction, and Coronary Artery Disease: Common Links. European Urology; Vol 52, Iss 6, Dec 2007:1590–1600. [link]
[240] Amaral S, Oliveira PJ, Ramalho-Santos J. Diabetes and the impairment of reproductive function: possible role of mitochondria and reactive oxygen species. Curr Diabetes Rev. 2008 Feb;4(1):46-54. [PubMed]

[241] Bleustein CB, Arezzo JC, Eckholdt H, Melman A. The neuropathy of erectile dysfunction. International Journal of Impotence Research; The Journal of Sexual Medicine; December 2002, Volume 14, Number 6, Pages 433-439. [link]
[242] Watson NF, Buchwald D, Goldberg J, Noonan C, Ellenbogen RG. Neurologic signs and symptoms in fibromyalgia. Arthritis Rheum. 2009 Sep;60(9):2839-44. doi: 10.1002/art.24772.
[PubMed]
[243] Bradley LA, McKendree-Smith NL, Alarcón GS, Cianfrini LR. Is fibromyalgia a neurologic disease? Curr Pain Headache Rep. 2002 Apr;6(2):106-14. [PubMed]
[244] Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008 Jan;58(1):26-35. doi: 10.1002/art.23176. [PubMed]
[245] Gallagher AM, Thomas JM, Hamilton WT, White PD .Incidence of fatigue symptoms and diagnoses presenting in UK primary care from 1990 to 2001. J R Soc Med. 2004 Dec; 97(12): 571–575. [link]
[246] Sacks JJ , Luo YH, Helmick CG. Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001-2005. Arthritis Care Res. 2010;62(4):460-4.
[247] Pall ML. NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. FASEB J; 2002 Sept; 16 (11):1407-1417. [link]
[248] Cordero MD, de Miguel M, Carmona-López I, Bonal P, Campa F, Moreno-Fernández AM. Oxidative stress and mitochondrial dysfunction in fibromyalgia. Neuro Endocrinol Lett. 2010;31(2):169-73. [PubMed]
[249] Bote ME, Garcia JJ, Hinchado MD, Ortega E. Fibromyalgia: Anti-Inflammatory and Stress Responses after Acute Moderate Exercise. PLoS One. 2013 Sep 4;8(9):e74524. [PubMed]
[250] Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: Application of power spectral analysis of heart rate variability. Seminars in Arthritis and Rheumatism; Volume 29, Issue 4, February 2000, Pages 217–227. [link]
[251] Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ, Finkelstein JA. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol. 2007; 5:1424-9.
[252] Hein R, Köster I, Bollschweiler E, Schubert I. Prevalence of inflammatory bowel disease: estimates for 2010 and trends in Germany from a large insurance-based regional cohort. Scand J Gastroenterol. 2014 Nov;49(11):1325-35. doi: 10.3109/00365521.2014.962605. Epub 2014 Sep 26. [PubMed]
[253] Centers for Disease Control and Prevention. An Expensive Disease Without a Cure. Accessed 2016 Feb 27. [CDC]
[254] Kappelman MD, Rifas-Shiman SL, Porter CQ, Ollendorf DA, Sandler RS, Galanko JA, Finkelstein JA.Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology. 2008 Dec;135(6):1907-13. doi: 10.1053/j.gastro.2008.09.012. Epub 2008 Sep 17. [PubMed]
[255] Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. Am J Physiol. 1996 Nov;271(5 Pt 1):C1424-37. [PubMed]
[256] Singer II, Kawka DW, Scott S, Weidner JR, Mumford RA, Riehl TE, Stenson WF. Expression of inducible nitric oxide synthase and nitrotyrosine in colonic epithelium in inflammatory bowel disease. Gastroenterology. 1996 Oct;111(4):871-85. [PubMed]
[257] Mabley JG, Liaudet L, Pacher P, Southan GJ, Groves JT, Salzman AL, Szabó C. Part II: beneficial effects of the peroxynitrite decomposition catalyst FP15 in murine models of arthritis and colitis. Mol Med. 2002 Oct;8(10):581-90. [PubMed]
[258] Mccafferty D. Peroxynitrite and inflammatory bowel disease. Gut. 2000 Mar; 46(3): 436–439. doi:10.1136/gut.46.3.436. [PubMed] [pdf]
[259] Kimura H, Hokari R, Miura S, Shigematsu T, Hirokawa M, Akiba Y, Kurose I, Higuchi H, Fujimori H, Tsuzuki Y, Serizawa H, Ishii H. Increased expression of an inducible isoform of nitric oxide synthase and the formation of peroxynitrite in colonic mucosa of patients with active ulcerative colitis. Gut. 1998 Feb;42(2):180-7. [PubMed]

[260] Keshavarzian A, Banan A, Farhadi A, Komanduri S, Mutlu E, Zhang Y, Fields JZ. Increases in free radicals and cytoskeletal protein oxidation and nitration in the colon of patients with inflammatory bowel disease. Gut. 2003 May;52(5):720-8. [PubMed]
[261] Kim YJ, Kim EH, Hahm KB. Oxidative stress in inflammation-based gastrointestinal tract diseases: challenges and opportunities. J Gastroenterol Hepatol. 2012 Jun;27(6):1004-10. [PubMed]
[262] Tanner AR, Arthur MJ, Wright R. Macrophage activation, chronic inflammation and gastrointestinal disease. Gut. 1984 Jul; 25(7): 760–783. [link]
[263] Novak EA, Mollen KP. Mitochondrial dysfunction in inflammatory bowel disease. Front Cell Dev Biol. 2015 Oct 1;3:62. doi: 10.3389/fcell.2015.00062. eCollection 2015. [PubMed]
[264] Beltrán B, Nos P, Dasí F, Iborra M, Bastida G, Martínez M, O'Connor JE, Sáez G, Moret I, Ponce J. Mitochondrial dysfunction, persistent oxidative damage, and catalase inhibition in immune cells of naïve and treated Crohn's disease. Inflamm Bowel Dis. 2010 Jan;16(1):76-86. doi: 10.1002/ibd.21027. [PubMed]
[265] Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. The Journal of Clinical Psychiatry [2001, 62 Suppl 8:28-36; discussion 37]. [link]
[266] Tu K, Chen Z, Lipscombe LL. Prevalence and incidence of hypertension from 1995 to 2005: a population-based study
CMAJ. 2008 May 20; 178(11): 1429–1435. (PubMed)
[267] Cohen JD. Hypertension Epidemiology and Economic Burden: Refining Risk Assessment To Lower Costs. Managed Care. October 2009. [pdf]
[268] Pall ML. Pulmonary Hypertension Is a Probable NO/ONOO− Cycle Disease: A Review. ISRN Hypertension. 2013; Art ID 742418:27 pps. http://dx.doi.org/10.5402/2013/742418. [link]
[269] Vaziri ND, Wang XQ, Oveisi F, Rad B. Induction of oxidative stress by glutathione depletion causes severe hypertension in normal rats. Hypertension. 2000 Jul;36(1):142-6. [PubMed] [FullText]
[270] Guzik TJ, West NE, Pillai R, Taggart DP, Channon KM. Nitric oxide modulates superoxide release and peroxynitrite formation in human blood vessels. Hypertension. 2002 Jun;39(6):1088-94. [PubMed] [FullText]
[271] Roberts CK, Vaziri ND, Ni Z, Barnard RJ. Correction of long-term diet-induced hypertension and nitrotyrosine accumulation by diet modification. Atherosclerosis. 2002 Aug;163(2):321-7. [PubMed]
[272] Harrison DG, Gongora MC. Oxidative stress and hypertension. Med Clin North Am. 2009 May;93(3):621-35. [PubMed]
[273] Li JJ, Chen JL. Inflammation may be a bridge connecting hypertension and atherosclerosis. Med Hypotheses. 2005;64(5):925-9. [PubMed]
[274] Puddu P, Puddu GM, Cravero E, De Pascalis S, Muscari A. The putative role of mitochondrial dysfunction in hypertension. Clin Exp Hypertens. 2007 Oct;29(7):427-34. [PubMed]
[275] Julius S. Autonomic nervous dysfunction in essential hypertension. Diabetes Care. 1991 Mar;14(3):249-59. [PubMed]
[276] Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012 Jul;62(1):160-5. doi: 10.1016/j.eururo.2012.03.052. Epub 2012 Mar 31.
[277] Romero V, Akpinar H, Assimos DG. Kidney Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors. Rev Urol. 2010 Spring-Summer; 12(2-3): e86–e96. [link]
[278] Hyams ES, Matlaga BR. Economic impact of urinary stones. Transl Androl Urol 2014;3(3):278-283. [link]
[279] Abbagani S, Gundimeda SD, Varre S, Ponnala D, Mundluru HP. Kidney Stone Disease: Etiology And Evaluation. Internat J of Applied Bio and Pharma Tech. 2010 May-July; 1(1):175-182. [pdf]
[280] Tsao KC, Wu TL, Chang PY, Sun CF, Wu LL, Wu JT. Multiple risk markers for atherogenesis associated with chronic inflammation are detectable in patients with renal stones. J. Clin. Lab. Anal. 2007; 21: 426–431. doi: 10.1002/jcla.20215 [PubMed]
[281] Ma MC, Chen YS, Huang HS. Erythrocyte oxidative stress in patients with calcium oxalate stones correlates with stone size and renal tubular damage. Urology. 2014 Feb;83(2):510.e9-17. doi: 10.1016/j.urology.2013.09.050. Epub 2013 Dec 19. [PubMed]

[282] Trinchieri A, Lizzano R, Castelnuovo C, Zanetti G, Pisani E. Urinary patterns of patients with renal stones associated with chronic inflammatory bowel disease. Arch Ital Urol Androl. 2002 Jun;74(2):61-4. [PubMed]
[283] Cao LC, Honeyman TW, Cooney R, Kennington L, Scheid CR, Jonassen JA. Mitochondrial dysfunction is a primary event in renal cell oxalate toxicity. Kidney Int. 2004 Nov;66(5):1890-900. [PubMed]
[284] Domingos F, Escalda A. Causes of autonomic dysfunction in idiopathic recurrent kidney stone formers. Int Urol Nephrol. 2012 Jun;44(3):873-82. doi: 10.1007/s11255-011-9983-0. Epub 2011 May 11. [PubMed]
[285] The National Institute of Diabetes and Digestive and Kidney Diseases. The Growing Burden of Kidney Disease. Kidney Disease Statistics for the United States. [link]
[286] The American Society of Nephrology. Kidney Disease: A Growing Public Health and Economic Concern. [pdf]
[287] Galli F. Protein damage and inflammation in uraemia and dialysis patients. Nephrol Dial Transplant. 2007 Jul;22 Suppl 5:v20-36. [PubMed] [FullText]
[288] Small DM, Coombes JS, Bennett N, Johnson DW, Gobe GC. Oxidative stress, anti-oxidant therapies and chronic kidney disease. Nephrology (Carlton). 2012 May;17(4):311-21. doi: 10.1111/j.1440-1797.2012.01572.x. [PubMed]
[289] Silverstein DM. Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease. Pediatr Nephrol. 2009 Aug;24(8):1445-52. doi: 10.1007/s00467-008-1046-0. Epub 2008 Dec 13. [PubMed]
[290] Che R, Yuan Y, Huang S, Zhang A. Mitochondrial dysfunction in the pathophysiology of renal diseases. Am J Physiol Renal Physiol. 2014 Feb 15;306(4):F367-78. doi: 10.1152/ajprenal.00571.2013. Epub 2013 Dec 4. [PubMed]
[291] Phillips JK. Autonomic Dysfunction in Heart Failure and Renal Disease. Front Physiol. 2012; 3: 219. [link]
[292] Caligaris-Cappio F. Inflammation, the microenvironment and chronic lymphocytic leukemia. Haematologica. 2011 Mar; 96(3): 353–355. doi : 10.3324/haematol.2010.039446 [PubMed]
[293] Giles FJ, Krawczyk J, O'Dwyer M, Swords R, Freeman C. The role of inflammation in leukaemia. Adv Exp Med Biol. 2014;816:335-60. doi: 10.1007/978-3-0348-0837-8_13. [PubMed]
[294] Surveillance, Epidemiology, and End Results Program. Trends in SEER Incidence and U.S. Mortality Using the Joinpoint Regression Program, 1975-2012 With up to Five Joinpoints, 1992-2012 With up to Three Joinpoints, Both Sexes by Race/Ethnicity Table 13.1: Leukemia. Turning Cancer Data Into Discovery. Accessed 2016 Feb 27. [link]
[295] Zhuang S, Simon G. Peroxynitrite-induced apoptosis involves activation of multiple caspases in HL-60 cells. Am J Physiol Cell Physiol. 2000 Aug;279(2):C341-51. [PubMed] [FULLTEXT]
[296] Wilt SG, Dugger NV, Hitt ND, Hoffman PM. Evidence for oxidative damage in a murine leukemia virus-induced neurodegeneration. J Neurosci Res. 2000 Nov 1;62(3):440-50. [PubMed]
[297] Jitschin R, Hofmann AD, Bruns H, Giessl A, Bricks J, Berger J, Saul D, Eckart MJ, Mackensen A, Mougiakakos D. Mitochondrial metabolism contributes to oxidative stress and reveals therapeutic targets in chronic lymphocytic leukemia. Blood. 2014 Apr 24;123(17):2663-72. [PubMed]
[298] Caligaris-Cappio F. Inflammation, the microenvironment and chronic lymphocytic leukemia. Haematologica. 2011 Mar; 96(3): 353–355. [link]
[299] Liu MJ, Wang Z, Li HX, Wu RC, Liu YZ, Wu QY. Mitochondrial dysfunction as an early event in the process of apoptosis induced by woodfordin I in human leukemia K562 cells. Toxicology and Applied Pharmacology Volume 194, Issue 2, 15 January 2004, Pages 141–155. [link]
[300] Kamath MV, Halton J, Harvey A, Turner-Gomes S, McArthur A, Barr RD. Cardiac autonomic dysfunction in survivors of acute lymphoblastic leukemia in childhood. Int J Oncol. 1998 Mar;12(3):635-40. [PubMed]
[301] Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcón GS, Winkelmayer WC, Costenbader KH. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum. 2013 Mar;65(3):753-63. doi: 10.1002/art.37795. [PubMed]

[302] Panopalis P, Yazdany J, Gillis JZ, Julian L, Trupin L, Hersh AO, Criswell LA, Katz P, Yelin E. Health care costs and costs associated with changes in work productivity among persons with systemic lupus erythematosus. Arthritis Rheum. 2008 Dec 15;59(12):1788-95. doi: 10.1002/art.24063. [PubMed]
[303] Avalos I, Chung CP, Oeser A, Milne GL, Morrow JD, Gebretsadik T, Shintani A, Yu C, Stein CM. Oxidative stress in systemic lupus erythematosus: relationship to disease activity and symptoms. Lupus. 2007;16(3):195-200. [PubMed]
[304] Muñoz LE, Janko C, Schulze C, Schorn C, Sarter K, Schett G, Herrmann M. Autoimmunity and chronic inflammation – two clearance-related steps in the etiopathogenesis of SLE. Autoimmun Rev. 2010 Nov;10(1):38-42. [PubMed]
[305] Perl A, Hanczko R, Doherty E. Assessment of mitochondrial dysfunction in lymphocytes of patients with systemic lupus erythematosus. Methods Mol Biol. 2012;900:61-89. [PubMed]
[306] Haupt HM, Hood AF, Cohen MH. Inflammatory melanoma. J Am Acad Dermatol. 1984 Jan;10(1):52-5. [PubMed]
[307] Maru GB, Gandhi K, Ramchandani A, Kumar G. The role of inflammation in skin cancer.
Adv Exp Med Biol. 2014;816:437-69. doi: 10.1007/978-3-0348-0837-8_17. [PubMed]
[308] SEER Cancer Statistics. [link]
[309] Guy GP Jr, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002- 2006 and 2007-2011. Am J Prev Med. 2015 Feb;48(2):183-7. doi: 10.1016/j.amepre.2014.08.036. Epub 2014 Nov 10. [PubMed]
[310] Ekmekcioglu S, Ellerhorst J, Smid CM, Prieto VG, Munsell M, Buzaid AC, Grimm EA. Inducible Nitric Oxide Synthase and Nitrotyrosine in Human Metastatic Melanoma Tumors Correlate with Poor Survival. Clin Cancer Res. 2000 Dec; 6: 4768. [link]
[311] Van Nieuwpoort FA, Out-Luiting C, de Snoo FA, Pavel S, Bergman W, Gruis NA. Does oxidative stress drive melanoma development? – new evidence from gene ontology studies. Department Of Dermatology, Leiden University Medical Centre. Chapter 5:90-117. [pdf]
[312] Meyer C, Sevko A, Ramacher M, Bazhin AV, Falk CS, Osen W, Borrello I, Kato M, Schadendorf D, Baniyash M, Umansky V. Chronic inflammation promotes myeloid-derived suppressor cell activation blocking antitumor immunity in transgenic mouse melanoma model. Proc Natl Acad Sci U S A. 2011 Oct 11;108(41):17111-6. [PubMed]
[313] Newton HB, M.D. Neurologic Complications of Systemic Cancer. Am Fam Physician. 1999 Feb 15;59(4):878- 886. [link]
[314] National Multiple Sclerosis Society. Estimating the prevalence of MS. [link]
[315] Zwibel HL, Smrtka J. Improving Quality of Life in Multiple Sclerosis: An Unmet Need. Am J Manag Care. 2011;17:S139-S145. [link]
[316] Hooper DC, Bagasra O, Marini JC, Zborek A, Ohnishi ST, Kean R, Champion JM, Sarker AB, Bobroski L, Farber JL, Akaike T, Maeda H, Koprowski H. Prevention of experimental allergic encephalomyelitis by targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. Proc Natl Acad Sci U S A. 1997 Mar 18;94(6):2528-33. [PubMed]
[317] Okuda Y, Sakoda S, Fujimura H, Yanagihara T. Nitric oxide via an inducible isoform of nitric oxide synthase is a possible factor to eliminate inflammatory cells from the central nervous system of mice with experimental allergic encephalomyelitis. J Neuroimmunol. 1997 Mar;73(1-2):107-16. [PubMed]
[318] Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. J Neurol. 2004 Mar;251(3):261-8. [PubMed]
[319] Fitzner D, Simons M. Chronic Progressive Multiple Sclerosis – Pathogenesis of Neurodegeneration and Therapeutic Strategies. Curr Neuropharmacol. 2010 Sep; 8(3): 305–315. [link]
[320] Brück W, Stadelmann C. Inflammation and degeneration in multiple sclerosis.Neurol Sci. 2003 Dec;24 Suppl 5:S265-7. [PubMed]
[321] Andrews HE, Nichols PP, Bates D, Turnbull DM. Mitochondrial dysfunction plays a key role in progressive axonal loss in Multiple Sclerosis. Curr Neuropharmacol. 2010 Sep; 8(3): 305–315. [link]
[322] Mao P, Reddy PH. Is multiple sclerosis a mitochondrial disease? Biochim Biophys Acta. 2010 Jan; 1802(1): 66–79. [PubMed]
[323] Haensch CA, Jörg J. Autonomic dysfunction in multiple sclerosis. J Neurol. 2006 Feb;253 Suppl 1:I3-9. [PubMed]

[324] Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011–2012. NCHS data brief, no 131. Hyattsville, MD: National Center forHealth Statistics. 2013. [link]
[325] Menifield CE, Doty N, Fletcher A. Obesity in America. ABNF J. 2008 Summer;19(3):83-8. [PubMed]
[326] Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011–2012. NCHS data brief, no 131. Hyattsville, MD: National Center forHealth Statistics. 2013. [link]
[327] Hammond RA, Levine R. The economic impact of obesity in the United States. Diabetes, metabolic syndrome and obesity : targets and therapy. 2010;3:285-295. doi:10.2147/DMSOTT.S7384. [PubMed]
[328] Jeevendra Martyn JA, Kaneki M, Yasuhara S. Obesity-Induced Insulin Resistance and Hyperglycemia: Etiological Factors and Molecular Mechanisms. Anesthesiology. 2008;109(1):137-148. doi:10.1097/ALN.0b013e3181799d45. [PubMed]
[329] Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH, Le Jemtel TH. Vascular inflammation in obesity and sleep apnea. Circulation. 2010 Mar 2;121(8):1014-21. doi: 10.1161/CIRCULATIONAHA.109.900357. Epub 2010 Feb 16. [PubMed]
[330] Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004 Dec 15; 114(12): 1752–1761. [link]
[331] Navarro JF, Mora C. Role of inflammation in diabetic complications. Nephrol. Dial. Transplant. (December 2005) 20 (12): 2601-2604. [link]
[332] Bournat JC, Brown CW. Mitochondrial dysfunction in obesity. Curr Opin Endocrinol Diabetes Obes. 2010 Oct;17(5):446-52. [PubMed]
[333] Laitinen T, Lindström J, Eriksson J, Ilanne-Parikka P, Aunola S, Keinänen-Kiukaanniemi S, Tuomilehto J, Uusitupa M. Cardiovascular autonomic dysfunction is associated with central obesity in persons with impaired glucose tolerance. Diabet Med. 2011 Jun;28(6):699-704. doi: 10.1111/j.1464-5491.2011.03278.x. [PubMed]
[334] Kelleher KJ, McInerny TK, Gardner WP, Childs GE, Wasserman RC. Increasing identification of psychosocial problems: 1979-1996. Pediatrics. 2000 Jun;105(6):1313-21. [PubMed]
[335] Hossain JL, Shapiro CM. The prevalence, cost implications, and management of sleep disorders: an overview. Sleep Breath. 2002 Jun;6(2):85-102. [PubMed]
[336] Franklin K, Lindberg E, Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea; J Thorac Dis. 2015 Aug; 7(8): 1311–1322.

[337] Institute of Medicine (US) Committee on Sleep Medicine and Research; Colten HR, Altevogt BM, editors. Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. Washington (DC): National Academies Press (US); 2006. 4, Functional and Economic Impact of Sleep Loss and Sleep-Related Disorders. [PubMed]
[338] Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, Gow A. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. Sleep. 2004 Mar 15;27(2):194-201. [PubMed]
[339] Patt BT, Jarjoura D, Haddad DN, Sen CK, Roy S, Flavahan NA, Khayat RN. Endothelial dysfunction in the microcirculation of patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2010 Dec 15;182(12):1540-5. doi: 10.1164/rccm.201002-0162OC. Epub 2010 Jul 23. [PubMed]
[340] Huang CC, Lai CJ, Tsai MH, Wu YC, Chen KT, Jou MJ, Fu PI, Wu CH, Wei IH. Effects of melatonin on the nitric oxide system and protein nitration in the hypobaric hypoxic rat hippocampus. BMC Neuroscience 2015, 16:61. [link]
[341] Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, Colombo PC, Basner RC, Factor P, LeJemtel TH. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation. 2008 Apr 29;117(17):2270-8. doi: 10.1161/CIRCULATIONAHA.107.741512. Epub 2008 Apr 14. [PubMed]
[342] Barreiro E, Nowinski A, Gea J, Sliwinski P. Oxidative stress in the external intercostal muscles of patients with obstructive sleep apnoea. Thorax 2007;62:1095-1101 doi:10.1136/thx.2006.069963 [PubMed]

[343] Gulec M, Ozkol H, Selvi Y, Tuluce Y, Aydin A, Besiroglu L, Ozdemir PG. Oxidative stress in patients with primary insomnia. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Jun 1;37(2):247-51. [PubMed]
[344] Lavie L. Obstructive sleep apnoea syndrome--an oxidative stress disorder. Sleep Med Rev. 2003 Feb;7(1):35-51. [PubMed]
[345] Noguti J, Andersen ML, Cirelli C, Ribeiro DA. Oxidative stress, cancer, and sleep deprivation: is there a logical link in this association? Sleep Breath. 2013 Sep;17(3):905-10. [PubMed]
[346] Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep Loss and Inflammation. Best Pract Res Clin Endocrinol Metab. 2010 Oct;24(5):775-84. [PubMed]
[347] Basta M, Chrousos GP, Vela-Bueno A, Vgontzas AN. Chronic Insomnia And Stress System. Sleep Med Clin. 2007 Jun; 2(2): 279–291. [PubMed]
[348] Calvin AD, Albuquerque FN, Lopez-Jimenez F, Somers VK. Obstructive Sleep Apnea, Inflammation, and the Metabolic Syndrome. Metab Syndr Relat Disord. 2009 Aug; 7(4): 271–277. [link]
[349] Emory University. "Poor sleep quality increases inflammation, community study finds." ScienceDaily. ScienceDaily, 15 November 2010. [link]
[350] Ramezani RJ, Stacpoole PW. Sleep disorders associated with primary mitochondrial diseases. J Clin Sleep Med. 2014 Nov 15;10(11):1233-9. [PubMed]
[351] Srinivasan V, Spence DW, Pandi-Perumal SR, Brown GM, Cardinali DP. Melatonin in Mitochondrial Dysfunction and Related Disorders. Int J Alzheimers Dis. 2011; 2011: 326320. [PubMed]
[352] Postuma RB, Lanfranchi PA, Blais H, Gagnon JF, Montplaisir JY. Cardiac autonomic dysfunction in idiopathic REM sleep behavior disorder. Movement Disorders; Volume 25, Issue 14, pages 2304–2310, 30 October 2010. [link]
[353] Mallien J, Isenmann S, Mrazek A, Haensch CA. Sleep Disturbances and Autonomic Dysfunction in Patients with Postural Orthostatic Tachycardia Syndrome. Front Neurol. 2014; 5: 118. doi: 10.3389/fneur.2014.00118 [PubMed]
[354] Benarroch EE, Stotz-Potter EH. Dysautonomia in fatal familial insomnia as an indicator of the potential role of the thalamus in autonomic control. Brain Pathol. 1998 Jul;8(3):527-30. [PubMed]
[355] National Institute of Neurological Disorders and Stroke. NINDS Sleep Apnea Information Page. Modified 2015 Oct 21. Accessed 2106 Mar 24. [link]
[356] Punjabi NM. The Epidemiology of Adult Obstructive Sleep Apnea. Proc Am Thorac Soc. 2008 Feb 15; 5(2):136–143. [link]
[357] Durmer J, Pryor J. The Thief In The Night: Stop Sleep Apnea From Robbing Your Company While You Sleep. Accessed 2016 Mar 13. [link]
[358] Woodson BT, Brusky LT, Saurajen A, Jaradeh S. Association of autonomic dysfunction and mild obstructive sleep apnea. Otolaryngol Head Neck Surg. 2004 Jun;130(6):643-8. [PubMed]
[359] Pallesen S, Sivertsen B, Nordhus IH, Bjorvatn B. A 10-year trend of insomnia prevalence in the adult Norwegian population. Sleep Med. 2014 Feb;15(2):173-9. [PubMed]
[360] Dohgramji K. Insomnia and Excessive Daytime Sleepiness (EDS) Merck Manual; Professional; Neurologic Disorders; Sleep and Wakefulness Disorders. Revised 2014 Oct. Accessed online 2016 Mar 24. [Link]
[361] Ford ES, Cunningham TJ, Giles WH, Croft JB. Trends in insomnia and excessive daytime sleepiness among U.S. adults from 2002 to 2012. Sleep Med. 2015 Mar;16(3):372-8. [PubMed]
[362] Skin Cancer Foundation. Squamous Cell Carcinoma – Causes and Risk Factors. Accessed 2016 Mar 24. [Link]
[363] Gasparoto TH1, de Oliveira CE, de Freitas LT, Pinheiro CR, Ramos RN, da Silva AL, Garlet GP, da Silva JS, Campanelli AP. Inflammatory events during murine squamous cell carcinoma development. J Inflamm (Lond). 2012 Nov 23;9(1):46. doi: 10.1186/1476-9255-9-46. [PubMed]
[364] Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013 Jun;68(6):957-66. [PubMed]
[365] Sepehr A, Tanière P, Martel-Planche G, Zia'ee AA, Rastgar-Jazii F, Yazdanbod M, Etemad-Moghadam G, Kamangar F, Saidi F, Hainaut P. Distinct pattern of TP53 mutations in squamous cell carcinoma of the esophagus in Iran.Oncogene; 2001 Nov 1;20(50):7368-7374. [link]

[366] Kato H, Miyazaki T, Yoshikawa M, Nakajima M, Fukai Y, Tajima K, Masuda N, Tsutsumi S, Tsukada K, Nakajima T, Kuwano H. Nitrotyrosine in esophageal squamous cell carcinoma and relevance to p53 expression. Cancer Letters. 2000 May 29; 153(1–2):121–127. [link]
[367] Bentz BG, Haines GK 3rd, Radosevich JA. Increased protein nitrosylation in head and neck squamous cell carcinogenesis. Head Neck. 2000 Jan;22(1):64-70. [PubMed]
[368] Kumar A, Pant MC, Singh HS, Khandelwal S. Determinants of oxidative stress and DNA damage (8-OhdG) in squamous cell carcinoma of head and neck. Indian J Cancer. 2012 Jul-Sep;49(3):309-15. [PubMed]
[369] Gasparoto TH, de Oliveira CE, de Freitas LT, Pinheiro CR, Ramos RN, da Silva AL, Garlet GP, da Silva, Campanelli AP. Inflammatory events during murine squamous cell carcinoma development. Journal of Inflammation 2012, 9:46. [link]
[370] Lai CH, Huang SF, Liao CT, Chen IH, HM, Hsieh LL. Clinical Significance in Oral Cavity Squamous Cell Carcinoma of Pathogenic Somatic Mitochondrial Mutations. PLoS One. 2013; 8(6): e65578. [link]
[371] Kanaji N, Watanabe N, Kita N, Bandoh S, Tadokoro A, Ishii T, Dobashi H, Matsunaga T. Paraneoplastic syndromes associated with lung cancer. World J Clin Oncol. 2014 Aug 10; 5(3): 197–223. Published online 2014 Aug 10. doi: 10.5306/wjco.v5.i3.197 [PubMed]
[372] Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, \Ferioli S, De Los Rios La Rosa F, Broderick JP, Kleindorfer DO. Age at stroke: Temporal trends in stroke incidence in a large, biracial population. Neurology. 2012 Oct 23; 79(17): 1781–1787. [PubMed]
[373] CDC. Stroke Facts. Accessed 2016 Feb 27.[CDC]
[374] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation. 2015;131:e29–e322. [LINK]
[375] Nanetti L, Taffi R, Vignini A, Moroni C, Raffaelli F, Bacchetti T, Silvestrini M, Provinciali L, Mazzanti L. Reactive oxygen species plasmatic levels in ischemic stroke. Mol Cell Biochem. 2007 Sep;303(1-2):19-25. Epub 2007 Mar 30. [PubMed]
[376] Allen CL, Bayraktutan U. Oxidative stress and its role in the pathogenesis of ischaemic stroke. Int J Stroke. 2009 Dec;4(6):461-70. [PubMed]
[377] Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol. 2010 May; 87(5):779-789. [link] [PubMed]
[378] Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2010 Jan; 1802(1): 80–91. [link]
[379] Korpelainen JT, Sotaniem i KA, Myllylä VV. Autonomic nervous system disorders in stroke. Clin Auton Res. 1999 Dec;9(6):325-33. [PubMed]
[380] NIH; National Institute of Diabetes and Digestive and Kidney Diseases. Endocrine & Metabolic Diseases A-Z. Accessed 2016 Mar. [Link]
[381] Leese GP, Flynn RV, Jung RT, Macdonald TM, Murphy MJ, Morris AD. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: The Thyroid Epidemiology Audit and Research Study (TEARS). Clin Endocrinol (Oxf). 2008 Feb;68(2):311-6. Epub 2007 Oct 29. [PubMed]
[382] Soni A. Use and Expenditures Related to Thyroid Disease among Women Age 18 and Older, U.S. Noninstitutionalized Population, 2008. MEPS; STATISTICAL BRIEF #348; 2011 Feb. Accessed 2016 Feb 27. [pdf]
[383] The Endocrine Society. Endocrine Facts and Figures: Thyroid. First Edition. 2015. Accessed 2016 Feb 27. [link]
[384] Franco MC, Antico Arciuch VG, Peralta JG, Galli S, Levisman D, López LM, Romorini L, Poderoso JJ, Carreras MC. Hypothyroid phenotype is contributed by mitochondrial complex I inactivation due to translocated neuronal nitric-oxide synthase. J Biol Chem. 2006 Feb 24;281(8):4779-86. Epub 2005 Dec 16. [PubMed]
[385] Rostami R, Aghasi MR, Mohammadi A, Nourooz-Zadeh J. Enhanced oxidative stress in Hashimoto's thyroiditis: inter- relationships to biomarkers of thyroid function. Clin Biochem. 2013 Mar;46(4-5):308-12. [PubMed]

[386] Türemen EE, Çetinarslan B, Sahin T, Cantürk Z, Tarkun I. Endothelial dysfunction and low grade chronic inflammation in subclinical hypothyroidism due to autoimmune thyroiditis. Endocr J. 2011; 58(5):349-354. [link]
[387] Siciliano G, Monzani F, Manca ML, Tessa A, Caraccio N, Tozzi G, Piemonte F, Mancuso M, Santorelli FM, Ferrannini E, Murri L.Human mitochondrial transcription factor A reduction and mitochondrial dysfunction in Hashimoto's hypothyroid myopathy. Mol Med. 2002 Jun;8(6):326-33. [PubMed]
[388] Kilic A, Gulgun M, Tascilar ME, Sari E, Yokusoglu M. Cardiac autonomic regulation is disturbed in children with euthyroid Hashimoto thyroiditis. Tohoku J Exp Med. 2012; 226(3):191-5. [PubMed]
[389] The Endocrine Society. Endocrine Facts and Figures: Thyroid. First Edition. 2015. Accessed 2016 Feb 27. [link]
[390] Schulz R, Dodge KL, Lopaschuk GD, Clanachan AS. Peroxynitrite impairs cardiac contractile function by decreasing cardiac efficiency. Am J Physiol Heart Circ Physiol. 1997; 272: H1212–H1219. [PubMed] [FullText]
[391] Floris R, Piersma SR, Yang G, Jones P, Wever R. Interaction of myeloperoxidase with peroxynitrite. A comparison with lactoperoxidase, horseradish peroxidase and catalase. Eur J Biochem. 1993; 215:767–775. [PubMed] [pdf]
[392] Sampson JB, Rosen H, Beckman JS. Peroxynitrite-dependent tyrosine nitration catalyzed by superoxide dismutase, myeloperoxidase, horseradish peroxidase. Methods Enzymol. 1996; 269: 210–218. [Link] [PubMed]
[393] Burner U, Furtmüller PG, Kettle AJ, Koppenol WH, Obinger C. Mechanism of reaction of myeloperoxidase with nitrite. J Biol Chem. 2000; 275: 20597–20601. [FullText] [PubFacts]
[394] Kettle AJ, van Dalen CJ, Winterbourn CC. Peroxynitrite and myeloperoxidase leave the same footprint in protein nitration. Redox Rep. 1997; 3: 257–258. [PubMed]
[395] Sampson JB, Ye Y, Rosen H, Beckman JS. Myeloperoxidase and horseradish peroxidase catalyze tyrosine nitration in proteins from nitrite and hydrogen peroxide. Arch Biochem Biophys. 1998; 356: 207–213. [PubMed]
[396] Murray J, Taylor SW, Zhang B, Ghosh SS, Capaldi RA. Oxidative damage to mitochondrial complex I due to peroxynitrite: identification of reactive tyrosines by mass spectrometry. J Biol Chem. 2003; 278: 37223–37230. [FullText] [PubMed]
[397] Radi R, Rodriguez M, Castro L, Telleri R. Inhibition of mitochondrial electron transport by peroxynitrite. Arch Biochem Biophys. 1994; 308: 89–95. [PubMed]
[398] MacMillan-Crow LA, Crow JP, Kerby JD, Beckman JS, Thompson JA. Nitration and inactivation of manganese superoxide dismutase in chronic rejection of human renal allografts. Proc Natl Acad Sci USA. 1996; 93:11853–11858. [PubMed]
[399] MacMillan-Crow LA, Cruthirds DL. Invited review: manganese superoxide dismutase in disease. Free Radic Res. 2001; 34: 325–336. [PubMed]
[400] MacMillan-Crow LA, Thompson JA. Tyrosine modifications and inactivation of active site manganese superoxide dismutase mutant (Y34F) by peroxynitrite. Arch Biochem Biophys. 1999; 366: 82–88. [PubMed]
[401] MacMillan-Crow LA, Cruthirds DL, Ahki KM, Sanders PW, Thompson JA. Mitochondrial tyrosine nitration precedes chronic allograft nephropathy. Free Radic Biol Med. 2001 Dec 15;31(12):1603-8. [PubMed]
[402] Aoyama K, Matsubara K, Fujikawa Y, Nagahiro Y, Shimizu K, Umegae N, Hayase N, Shiono H, Kobayashi S. Nitration of manganese superoxide dismutase in cerebrospinal fluids is a marker for peroxynitrite-mediated oxidative stress in neurodegenerative diseases. Ann Neurol. 2000; 47: 524–527. [PubMed]
[403] Xu S, Ying J, Jiang B, Guo W, Adachi T, Sharov V, Lazar H, Menzoian J, Knyushko TV, Bigelow D, Schoneich C, Cohen RA. Detection of sequence-specific tyrosine nitration of manganese SOD and SERCA in cardiovascular disease and aging. Am J Physiol Heart Circ Physiol. 2006; 290: H2220–H2227. [FullText]
[404] Knight-Lozano CA, Young CG, Burow DL, Hu ZY, Uyeminami D, Pinkerton KE, Ischiropoulos H, Ballinger SW. Cigarette smoke exposure and hypercholesterolemia increase mitochondrial damage in cardiovascular tissues. Circulation. 2002 Feb 19;105(7):849-54. [PubMed] [FullText]
[405] van der Loo B, Labugger R, Skepper JN, Bachschmid M, Kilo J, Powell JM, Palacios-Callender M, Erusalimsky JD, Quaschning T, Malinski T, Gygi D, Ullrich V, Lüscher TF. Enhanced peroxynitrite formation is associated with vascular aging. J Exp Med. 2000 Dec 18;192(12):1731-44. [PubMed]

[406] Schopfer FJ, Baker PR, Freeman BA. NO-dependent protein nitration: a cell signaling event or an oxidative inflammatory response? Trends Biochem Sci. 2003 Dec;28(12): 646–654. [PubMed]
[407] Pacher P, Schulz R, Liaudet L, Szabó C. Nitrosative stress and pharmacological modulation of heart failure. Trends Pharmacol Sci. 2005 Jun;26(6):302-10. [PubMed]
[408] Turko IV, Murad F. Protein nitration in cardiovascular diseases. Pharmacol Rev. 2002 Dec;54(4):619-34. [PubMed] [FullText]
[409] Lee WH, Gounarides JS, Roos ES, Wolin MS. Influence of peroxynitrite on energy metabolism and cardiac function in a rat ischemia-reperfusion model. Am J Physiol Heart Circ Physiol. 2003 Oct;285(4):H1385-95. Epub 2003 Jun 19. [PubMed] [FullText]
[410] Mihm MJ, Bauer JA. Peroxynitrite-induced inhibition and nitration of cardiac myofibrillar creatine kinase. Biochimie. 2002 Oct;84(10):1013-9. [PubMed]
[411] Mihm MJ, Coyle CM, Schanbacher BL, Weinstein DM, Bauer JA. Peroxynitrite induced nitration and inactivation of myofibrillar creatine kinase in experimental heart failure. Cardiovasc Res. 2001 Mar;49(4):798-807. [PubMed] [FullText]
[412] Mihm MJ, Yu F, Weinstein DM, Reiser PJ, Bauer JA. Intracellular distribution of peroxynitrite during doxorubicin cardiomyopathy: evidence for selective impairment of myofibrillar creatine kinase. Br J Pharmacol. 2002 Feb;135(3):581-8. [PubMed]
[413] Lokuta AJ, Maertz NA, Meethal SV, Potter KT, Kamp TJ, Valdivia HH, Haworth RA.Increased nitration of sarcoplasmic reticulum Ca2+-ATPase in human heart failure. Circulation. 2005 Mar 1;111(8):988-95. Epub 2005 Feb 14. [PubMed] [FullText]
[414] Li H, Gutterman DD, Rusch NJ, Bubolz A, Liu Y. Nitration and functional loss of voltage-gated K+ channels in rat coronary microvessels exposed to high glucose. Diabetes. 2004 Sep;53(9):2436-42. [PubMed] [FullText]
[415] Andrekopoulos C[1], Zhang H, Joseph J, Kalivendi S, Kalyanaraman B. Bicarbonate enhances alpha-synuclein oligomerization and nitration: intermediacy of carbonate radical anion and nitrogen dioxide radical. Biochem J. 2004 Mar 1;378(Pt 2):435-47.
[416] Giasson BI[1], Duda JE, Murray IV, Chen Q, Souza JM, Hurtig HI, Ischiropoulos H, Trojanowski JQ, Lee VM. Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. Science. 2000 Nov 3;290(5493):985-9. [PubMed]
[417] Przedborski S, Chen Q, Vila M, Giasson BI, Djaldatti R, Vukosavic S, Souza JM, Jackson-Lewis V, Lee VM, Ischiropoulos H. Oxidative post-translational modifications of alpha-synuclein in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. J Neurochem. 2001 Jan;76(2):637-40. [PubMed] [FullText]
[418] Blanchard-Fillion B, Souza JM, Friel T, Jiang GC, Vrana K, Sharov V, Barrón L, Schöneich C, Quijano C, Alvarez B, Radi R, Przedborski S, Fernando GS, Horwitz J, Ischiropoulos H. Nitration and inactivation of tyrosine hydroxylase by peroxynitrite. J Biol Chem. 2001 Dec 7;276(49):46017-23. Epub 2001 Oct 5. [PubMed] [FullText]
[419] Kuhn DM, Geddes TJ. Reduced nicotinamide nucleotides prevent nitration of tyrosine hydroxylase by peroxynitrite. Brain Res. 2002 Apr 12;933(1):85-9. [PubMed]
[420] Kuhn DM, Sadidi M, Liu X, Kreipke C, Geddes T, Borges C, Watson JT. Peroxynitrite-induced nitration of tyrosine hydroxylase: identification of tyrosines 423, 428, and 432 as sites of modification by matrix-assisted laser desorption ionization time-of-flight mass spectrometry and tyrosine-scanning mutagenesis. J Biol Chem. 2002 Apr 19;277(16):14336-42. Epub 2002 Feb 7. [PubMed] [FullText]
[421] Park S, Geddes TJ, Javitch JA, Kuhn DM. Dopamine prevents nitration of tyrosine hydroxylase by peroxynitrite and nitrogen dioxide: is nitrotyrosine formation an early step in dopamine neuronal damage? J Biol Chem. 2003 Aug 1;278(31):28736-42. Epub 2003 May 27. [PubMed] [FullText]
[422] Reynolds MR, Lukas TJ, Berry RW, Binder LI. Peroxynitrite-mediated tau modifications stabilize preformed filaments and destabilize microtubules through distinct mechanisms.
Biochemistry. 2006 Apr 4;45(13):4314-26. [PubMed]
[423] Crow JP, Ye YZ, Strong M, Kirk M, Barnes S, Beckman JS. Superoxide dismutase catalyzes nitration of tyrosines by peroxynitrite in the rod and head domains of neurofilament-L.

J Neurochem. 1997 Nov;69(5):1945-53. [PubMed]
[424] Banan A, Fields JZ, Decker H, Zhang Y, Keshavarzian A. Nitric oxide and its metabolites mediate ethanol-induced microtubule disruption and intestinal barrier dysfunction.
J Pharmacol Exp Ther. 2000 Sep;294(3):997-1008. [PubMed] [Fulltext]
[425] Tedeschi G, Cappelletti G, Negri A, Pagliato L, Maggioni MG, Maci R, Ronchi S. Characterization of nitroproteome in neuron-like PC12 cells differentiated with nerve growth factor: identification of two nitration sites in alpha-tubulin.
Proteomics. 2005 Jun;5(9):2422-32. [PubMed]
[426] Chang W, Webster DR, Salam AA, Gruber D, Prasad A, Eiserich JP, Bulinski JC. Alteration of the C-terminal amino acid of tubulin specifically inhibits myogenic differentiation. J Biol Chem. 2002 Aug 23;277(34):30690-8. Epub 2002 Jun 17. [PubMed] [FullText]
[427] Kasina S, Rizwani W, Radhika KV, Singh SS. Nitration of profilin effects its interaction with poly (l-proline) and actin. J Biochem. 2005; 138: 687–695. [FullText]
[428] Kasina S, Wasia R, Fasim A, Radhika KV, Singh SS. Phorbol ester mediated activation of inducible nitric oxide synthase results in platelet profilin nitration. Nitric Oxide. 2006 Feb;14(1):65-71. Epub 2005 Nov 8. [PubMed]
[429] Neumann P, Gertzberg N, Vaughan E, Weisbrot J, Woodburn R, Lambert W, Johnson A. Peroxynitrite mediates TNF-alpha-induced endothelial barrier dysfunction and nitration of actin. Am J Physiol Lung Cell Mol Physiol. 2006 Apr;290(4):L674-L684. Epub 2005 Nov 11.
[PubMed] [FullText]
[430] Clements MK, Siemsen DW, Swain SD, Hanson AJ, Nelson-Overton LK, Rohn TT, Quinn MT. Inhibition of actin polymerization by peroxynitrite modulates neutrophil functional responses.
J Leukoc Biol. 2003 Mar;73(3):344-55. [PubMed] [FullText]
[431] Mallozzi C, Di Stasi AM, Minetti M. Peroxynitrite modulates tyrosine-dependent signal transduction pathway of human erythrocyte band 3. FASEB J. 1997 Dec;11(14):1281–1290. [PubMed][pdf]
[432] Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci USA. 1990; 87: 1620–1624. [PubMed]
[433] Darley-Usmar VM, Hogg N, O'Leary VJ, Wilson MT, Moncada S. The simultaneous generation of superoxide and nitric oxide can initiate lipid peroxidation in human low density lipoprotein. Free Radic Res Commun. 1992; 17: 9–20. [PubMed]
[434] Hogg N, Darley-Usmar VM, Wilson MT, Moncada S. Production of hydroxyl radicals from the simultaneous generation of superoxide and nitric oxide. Biochem J. 1992; 281: 419–424. [PubMed]
[435] Radi R, Beckman JS, Bush KM, Freeman BA. Peroxynitrite-mediated sulfhydryl oxidation: the cytotoxic potential of superoxide and nitric oxide. J Biol Chem. 1991; 266: 4244–4250. [link] [pdf]
[436] Castro L, Rodriguez M, Radi R. Aconitase is readily inactivated by peroxynitrite, but not by its precursor, nitric oxide. J Biol Chem. 1994; 269: 29409–29415. [link] [pdf] [PubMed]
[437] Crow JP, Beckman JS, McCord JM. Sensitivity of the essential zinc-thiolate moiety of yeast alcohol dehydrogenase to hypochlorite and peroxynitrite. Biochemistry. 1995; 34: 3544–3552. [PubMed]
[438] Takakura K, Beckman JS, MacMillan-Crow LA, Crow JP. Rapid and irreversible inactivation of protein tyrosine phosphatases PTP1B, CD45, LAR by peroxynitrite. Arch Biochem Biophys. 1999; 369: 197–207. [PubMed]
[439] Arteel GE, Briviba K, Sies H. Protection against peroxynitrite. FEBS Lett. 1999 Feb 26;445(2-3):226-30. [PubMed]
[440] Cuzzocrea S, Costantino G, Mazzon E, Caputi AP. Protective effect of N-acetylcysteine on multiple organ failure induced by zymosan in the rat. Crit Care Med. 1999 Aug;27(8):1524-32. [PubMed]

[441] Cuzzocrea S, Zingarelli B, O'Connor M, Salzman AL, Szabó C. Effect of L-buthionine-(S,R)-sulphoximine, an inhibitor of gamma-glutamylcysteine synthetase on peroxynitrite- and endotoxic shock-induced vascular failure. Br J Pharmacol. 1998 Feb;123(3):525-37. [PubMed]
[442] Marshall KA, Reist M, Jenner P, Halliwell B. The neuronal toxicity of sulfite plus peroxynitrite is enhanced by glutathione depletion: implications for Parkinson's disease.
Free Radic Biol Med. 1999 Sep;27(5-6):515-20. [PubMed]
[443] Vargas MR, Pehar M, Cassina P, Beckman JS, Barbeito L. Increased glutathione biosynthesis by Nrf2 activation in astrocytes prevents p75NTR-dependent motor neuron apoptosis.
J Neurochem. 2006 May;97(3):687-96. Epub 2006 Mar 8. [PubMed] [FullText]
[444] Augusto O, Bonini MG, Amanso AM, Linares E, Santos CC, De Menezes SL. Nitrogen dioxide and carbonate radical anion: two emerging radicals in biology. Free Radic Biol Med. 2002; 32: 841–859. [PubMed]
[445] Alvarez B, Radi R. Peroxynitrite reactivity with amino acids and proteins. Amino Acids. 2003; 25: 295–311. [PubMed]
[446] Michelson AM, Maral J. Carbonate anions: effects on the oxidation of luminol, oxidative hemolysis, γ-irradiation and the reaction of activated oxygen species with enzymes containing various active centres.Biochomie. 1983; 65: 95–104. [PubMed]
[447] Cassina AM, Hodara R, Souza JM, Thomson L, Castro L, Ischiropoulos H, Freeman BA, Radi R. Cytochrome c nitration by peroxynitrite. J Biol Chem. 2000 Jul 14;275(28):21409-15. [PubMed] [FullText]
[448] Jang B, Han S. Biochemical properties of cytochrome c nitrated by peroxynitrite. Biochimie. 2006 Jan;88(1):53-8. Epub 2005 Jul 11. [PubMed]
[449] Radi R, Beckman JS, Bush KM, Freeman BA. Peroxynitrite oxidation of sulfhydryls. The cytotoxic potential of superoxide and nitric oxide. J Biol Chem. 1991. 266:4244–4250. [pdf]
[450] Ducrocq C, Blanchard B, Pignatelli B, Ohshima H. Peroxynitrite: an endogenous oxidizing and nitrating agent. Cell Mol Life Sci. 1999 Jul;55(8-9):1068-77.[PubMed]
[451] Bohle DS, Hansert B, Paulson SC, Smith BD. Biomemetic synthesis of the putative cytotoxin peroxynitrite, ONOO-, and its characterization as a tetramethylammonium salt. J Am Chem Soc. 1994; 116: 7423–7424. [link]
[452] Herold S, Exner M, Boccini F. The mechanism of the peroxynitrite-mediated oxidation of myoglobin in the absence and presence of carbon dioxide. Chem Res Toxicol. 2003; 16: 390–402. [PubMed]
[453]Thomson L, Trujillo M, Telleri R, Radi R.Kinetics of cytochrome c2+ oxidation by peroxynitrite: implications for superoxide measurements in nitric oxide-producing biological systems. Arch Biochem Biophys. 1995 Jun 1;319(2):491-7. [PubMed]
[454] Berlett BS, Levine RL, Stadtman ER. Carbon dioxide stimulates peroxynitrite-mediated nitration of tyrosine residues and inhibits oxidation of methionine residues of glutamine synthetase: both modifications mimic effects of adenylylation. Proc Natl Acad Sci U S A. 1998 Mar 17;95(6):2784-9. [PubMed] [FullText]
[455] Khor HK, Fisher MT, Schöneich C. Potential role of methionine sulfoxide in the inactivation of the chaperone GroEL by hypochlorous acid (HOCl) and peroxynitrite (ONOO-). J Biol Chem. 2004 May 7;279(19):19486-93. Epub 2004 Feb 2. [PubMed] [FullText]
[456] Whiteman M1, Kaur H, Halliwell B. Protection against peroxynitrite dependent tyrosine nitration and alpha 1-antiproteinase inactivation by some anti-inflammatory drugs and by the antibiotic tetracycline. Ann Rheum Dis. 1996 Jun;55(6):383-7. [PubMed] [pdf]
[457] Stadtman ER, Moskovitz J, Levine RL. Oxidation of methionine residues of proteins: biological consequences. Antioxid Redox Signal. 2003 Oct;5(5):577-82. [PubMed]
[458] Alvarez B, Demicheli V, Durán R, Trujillo M, Cerveñansky C, Freeman BA, Radi R. Inactivation of human Cu,Zn superoxide dismutase by peroxynitrite and formation of histidinyl radical. Free Radic Biol Med. 2004 Sep 15;37(6):813-22. [PubMed]
[459] Yamakura F, Ikeda K. Modification of tryptophan and tryptophan residues in proteins by reactive nitrogen species. Nitric Oxide. 2006 Mar;14(2):152-61. Epub 2005 Sep 2. [PubMed]

[460] Yamakura F1, Matsumoto T, Ikeda K, Taka H, Fujimura T, Murayama K, Watanabe E, Tamaki M, Imai T, Takamori K. Nitrated and oxidized products of a single tryptophan residue in human Cu,Zn-superoxide dismutase treated with either peroxynitrite-carbon dioxide or myeloperoxidase-hydrogen peroxide-nitrite. J Biochem. 2005 Jul;138(1):57-69. [PubMed] [FullText]
[461] Filep JG, Beauchamp M, Baron C, Paquette Y. Peroxynitrite mediates IL-8 gene expression and production in lipopolysaccharide-stimulated human whole blood. J Immunol. 1998; 161: 5656–5662. [PubMed] [FullText]
[462] Jozsef L, Khreiss T, El Kebir D, Filep JG. Activation of TLR-9 induces IL-8 secretion through peroxynitrite signaling in human neutrophils. J Immunol. 2006; 176: 1195–1202. [PubMed] [FullText]
[463] Khreiss T, Jozsef L, Potempa LA, Filep JG. Loss of pentameric symmetry in C-reactive protein induces interleukin-8 secretion through peroxynitrite signaling in human neutrophils. Circ Res.2005; 97: 690–697. [PubMed] [FullText]
[464] Zouki C, Jozsef L, Ouellet S, Paquette Y, Filep JG. Peroxynitrite mediates cytokine-induced IL-8 gene expression and production by human leukocytes. J Leukoc Biol. 2001; 69: 815–824. [PubMed] [FullText]
[465] Matata BM, Galinanes M. Peroxynitrite is an essential component of cytokines production mechanism in human monocytes through modulation of nuclear factor-kappa B DNA binding activity. J Biol Chem. 2002; 277:2330–2335. [PubMed] [FullText]
[466]Haddad IY, Ischiropoulos H, Holm BA, Beckman JS, Baker JR, Matalon S. Mechanisms of peroxynitrite-induced injury to pulmonary surfactants. Am J Physiol. 1993 Dec;265(6 Pt 1):L555-64.
[467] Low SY, Sabetkar M, Bruckdorfer KR, Naseem KM. The role of protein nitration in the inhibition of platelet activation by peroxynitrite. FEBS Lett. 2002; 511: 59–64. [PubMed] [FullText]
[468] Mondoro TH, Shafer BC, Vostal JG. Peroxynitrite-induced tyrosine nitration and phosphorylation in human platelets. Free Radic Biol Med. 1997; 22: 1055–1063. [PubMed]

Research Note: I want to offer my sincere gratitude and thanks to Wendy Odhner and others who tirelessly helped compile the research for this paper.

Selected Generational Growth Statistics reflecting the dramatic rise of twelve chronic diseases and conditions.

New Age of Chronic Disease:		Selected Generation Growth	
Autism	**+ 2094%**	**Alzheimer's**	**+ 299%**
Diabetes	**+ 305%**	**Autoimmune**	**+ 221%**

Sleep Apnea	**+ 430%**	**ADHD**	**+ 819%**
Bipolar Disorder	**+10833%**	**Asthma**	**+ 142%**
Osteoarthritis	**+ 449%**	**Fibromyalgia**	**+ 7727%**
Depression	**+ 280%**	**Hypothyroidism**	**+ 702%**

View publication stats